FDA Executive Summary

Prepared for the
June 13, 2012 meeting of the
Circulatory System Devices Panel

P110021

Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories:

1. RetroFlex 3™ Delivery System, models 9120FS23 and 9120FS26;
2. RetroFlex™ Balloon Catheter, models 9120BC20 and 9120BC23;
3. Ascendra™ Balloon Catheter, models 9100BCL23 and 9100BCL26;
4. Ascendra™ Balloon Aortic Valvuloplasty Catheter, model 9100BAVC;
5. Ascendra™ Introducer Sheath Set, model 9100IS; and
6. Crimper, models 9100CR23 and 9100CR26

INTRODUCTION

This is the FDA Executive Summary for a first-of-a-kind transcatheter aortic heart valve for patients who are at high risk for surgery, with a greater than or equal to 15% (high) risk of mortality for surgical aortic valve replacement. The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories have been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under Premarket Approval (PMA) application P110021, which is the subject of this Advisory Panel meeting. This device was previously reviewed by FDA for inoperable patients and was approved for this specific patient population on November 2, 2011.

This memorandum will summarize the FDA's review of the PMA up to this point, highlighting the particular areas for which we are seeking your expertise and input. These topics will include the results of the randomized clinical study conducted by the sponsor and the proposed post-approval study. At the conclusion of your review and discussion of the data presented, the Agency will ask for your recommendation regarding whether or not the benefits outweigh the risks of the device for the intended patient population.

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1. PROPOSED INDICATIONS FOR USE

TRANSFEMORAL PROCEDURE

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for patients with severe symptomatic native aortic valve stenosis who have been examined by a heart team including a cardiac surgeon and found to be:

- inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis, or

- operative candidates for aortic valve replacement but who are at a greater than or equal to 15% (high) risk of mortality for surgical aortic valve replacement.

The RetroFlex Balloon Catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

TRANSAPICAL PROCEDURE

The Edwards SAPIEN Transcatheter Heart Valve, Model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical delivery in patients with severe symptomatic native aortic valve stenosis who have been examined by a heart team including a cardiac surgeon and found to be operative candidates for aortic valve replacement but who are at a greater than or equal to 15% (high) risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Aortic Valvuloplasty Catheter is indicated for valvuloplasty of a stenotic native aortic valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The Ascendra Introducer Sheath Set is indicated for the introduction and removal of interventional devices used with the Edwards SAPIEN Transcatheter Heart Valve.

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

2. DEVICE DESCRIPTION

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories implant system consists of eight components and sub-components.

The Edwards SAPIEN Transcatheter Heart Valve consists of a heterologous (bovine) pericardium leaflet valve sutured within a stainless steel mesh frame, with a polyester skirt. It is offered in two sizes, 23 mm and 26 mm.

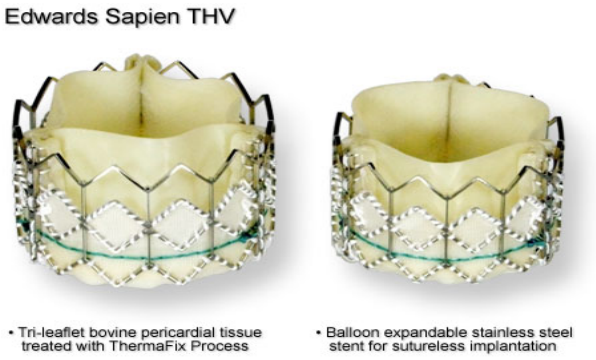


Figure 1 - Edwards SAPIEN THV

For a description of the other components of the system, please refer to the sponsor's Executive Summary.

3. REGULATORY HISTORY

The SAPIEN Transcatheter Heart Valve (THV) was originally manufactured by Percutaneous Valve Technologies (PVT), and was called the PHV Model 9000. Edwards Lifesciences acquired PVT in January 2004, changing the name of the device to Cribier-Edwards Aortic Bioprosthesis before changing the name again to SAPIEN THV. The SAPIEN THV has been the subject of 2 feasibility studies and 2 pivotal studies in the United States. There has also been extensive commercial use of the device outside of the US (OUS).

3.1 Pre-Market Approval of SAPIEN THV for Inoperable Patients (Cohort B)

A separate IDE study was performed using this same device in an inoperable patient population (Cohort B). This was the subject of P100041, which was reviewed by the Circulatory System Devices Panel on July 20, 2011. That PMA was approved on November 2, 2011.

3.2 Clinical Data Obtained OUS

There have been several studies involving the SAPIEN valve that were conducted OUS, including the REVIVE II (non-IDE OUS transfemoral study); the PARTNER EU (non-IDE OUS study); and the TRAVERCE (non-IDE transapical OUS study). The SAPIEN valve has also been used in the Canadian Special Access Program study.

3.3 United States Feasibility Studies

The REVIVAL I study was approved by FDA on January 26, 2005 to evaluate SAPIEN THV in a clinical setting by comparing transcatheter aortic valve replacement (TAVR) using SAPIEN THV versus balloon aortic valvuloplasty (BAV) and allowed either a retrograde (transfemoral) or antegrade implantation technique of a size 23 mm valve at two investigational sites. Enrollment began on March 10, 2005 and 5 roll-in subjects were enrolled at the William Beaumont Hospital and two at the Columbia University Medical Center, all with the antegrade approach. Of these, three expired, two valves migrated, and there was one stroke. After 7 antegrade implants, the study was suspended while a root cause analysis of the early failures and deaths was performed, major design modifications were made, and a comprehensive training program was instituted. The device was redesigned to include the addition of a 26 mm size valve, a new retrograde delivery catheter, replacement of equine tissue with bovine tissue valve leaflets, and the addition of the TFX anti-calcification treatment used on other Edwards valves.

The REVIVAL II study was then approved for 55 transfemoral and eventually 40 transapical subjects enrolled into a registry. The first subject was enrolled on December 15, 2005. After all of the transfemoral subjects were enrolled, the transapical approach was proposed for subjects with inadequate vessel size or ileo-femoral occlusive disease that did not allow transfemoral implantation of the valve. This study was performed to develop a greater understanding of the patient population and implant technique prior to beginning the PARTNER pivotal study.

3.4 United States Pivotal Study

The US pivotal trial consisted of two independent studies; an arm randomizing high risk, operable patients to either open surgical aortic valve replacement (AVR) or TAVR using the SAPIEN THV (Cohort A), and an arm randomizing inoperable patients to either "standard" therapy control arm or the SAPIEN THV (Cohort B). The pivotal study was later expanded to include the transapical subjects in the arm of the study enrolling operable patients (Cohort A), but not in the inoperable arm (Cohort B) at the request of the sponsor.

The PARTNER study was conditionally approved to begin in March 2007 (transfemoral only) for up to 40 subjects in Cohorts A and B, and was later expanded to add transapical insertion in December 2007, with an ultimate sample size of 1040 subjects (690 in Cohort A, 350 in Cohort B), at up to 30 sites. The PARTNER trial was a prospective, randomized (1:1), controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV in a stratified population of high risk patients.

The sponsor addressed all outstanding deficiencies to obtain unconditional approval on March 23, 2009 which included the statistical analysis plan.

The PMA and data addressed by this document contains the results of the Cohort A study only (high risk, operable patients).

3.5 Continued Access Protocol (CAP) Patients

The assessment of SAPIEN THV in the high risk, operable patient population data includes a combination of PARTNER IDE study data and Continued Access Protocol (CAP) data. In order to allow for continued access to a device when there may be a gap between trial completion and final regulatory review, sponsors have the opportunity to request additional patients who are still subject to the same patient protection measures as the IDE trial; such patients are enrolled into an "extension" of the initially approved sample size. This cohort is known as the "CAP" patients. The CAP is a single-arm registry with no comparator and may represent a different patient population.

4. PRE-CLINICAL STUDIES

The sponsor conducted thorough pre-clinical evaluations including extensive bench testing and animal studies. A brief description of the testing performed is enumerated below.

4.1 *In Vitro* Testing

The sponsor conducted *in vitro* performance and characterization studies of the SAPIEN THV under P100041:

1) Test results demonstrated that the device is compliant with FDA recognized international standards for biocompatibility.
2) Packaging and sterilization processes were validated according to FDA recognized international standards.
3) The valve was evaluated for MRI compatibility.
4) FDA performed a comprehensive review of the pre-clinical bench testing performed under challenging conditions to verify the design of the SAPIEN THV.
    a. Testing included fatigue (15 years of simulated use) and corrosion evaluation of the stainless steel valve frame as well as an assessment of hydrodynamic performance and durability (5 years of simulated use) of the whole valve.
    b. Scope of the bench testing performed exceeded that for traditional surgical bioprosthetic heart valves, and the results supported device safety in the anticipated clinical environment for the intended patient population.
5) Design verification testing of the accessories associated with transfemoral delivery was done using various voluntary standards, and was found to be acceptable.

The only new test data submitted under P110021 was bench testing of the Ascendra delivery system for the transapical delivery. This testing was found acceptable.

FDA Comment: FDA has no remaining concerns regarding the pre-clinical bench testing.

4.2 Valve-in-Valve Implantation

Since the availability of the TAVR procedure, clinicians have explored the clinical benefit of implanting the transcatheter heart valve into a dysfunctional bioprosthetic valve. There are no

pre-clinical data, *in vivo* animal data, and limited clinical data to fully understand the effects on the design of the device as well as the overall impact to the patient.

According to ISO 5840, surface damage (i.e., fretting corrosion) may occur between two surfaces that are in close contact, under pressure, and are subjected to slight relative motion, and corrosion (i.e., galvanic corrosion) could occur between two dissimilar materials. In addition to fretting corrosion and galvanic corrosion, other unknowns associated with valve-in-valve implantation may include long-term durability, valve migration/embolization, and access to the coronary ostia. The literature has reported many cases of valve-in-valve implantation involving the SAPIEN valve, such as SAPIEN in SAPIEN[1,2], SAPIEN in another transcatheter valve[3], and SAPIEN in a previously implanted surgical bioprosthesis[4-9] In the present study, the valve-in-valve configuration was used two times. There were SAPIEN valve in SAPIEN valve and resulted from device/procedure failure. There were no SAPIEN valves in surgical or prior bioprosthetic valves in the PARTNER trial. As transcatheter valve technologies become commercially available, widespread use of the valve-in-valve technique might occur.

FDA Comment: FDA believes that the safety and effectiveness of valve-in-valve implantation remains an unanswered question for this type of technology. With limited data available to draw any conclusions regarding the short-term and long-term effects of safety and effectiveness, FDA believes that these data could be captured in a post-approval study.

4.3 Preclinical *In Vivo* Testing of SAPIEN THV

The sponsor conducted preclinical *in vivo* performance and characterization studies of the SAPIEN valve and delivery system, which included the following:

1) Several feasibility studies, using the equine tissue version of the valve, in various animal models to determine the optimal model.
2) A Good Laboratory Practices (GLP) study, involving 19 sheep with induced aortic insufficiency (Hufnagel Model), into which the SAPIEN valve as implanted (either percutaneously or surgically) in the proximal descending aorta. Six animals survived to 21 weeks. The gross findings and histopathology results suggest that the valve is capable of long-term implant. This study also involved the equine version of the valve.
3) A second GLP study involving 21 sheep into which the SAPIEN was balloon deployed in an open chest operation into a modified Cosgrove Annuloplasty ring pre-sewn at the aortic annulus supra-annular position. The control valve (Carpentier-Edwards PERIMOUNT) was implanted in the same position. Both the treatment valve and the control valve had acceptable hemodynamic performance, normal healing with pliable leaflets, and no thrombus. In addition, there was no evidence of infection or calcification. These two valve models were comparable in all parameters evaluated. This final GLP study utilized the current bovine version of the valve which was studied in the PARTNER trial and is the subject of this PMA.

FDA Comment: There are no concerns regarding the animal study data provided to FDA.

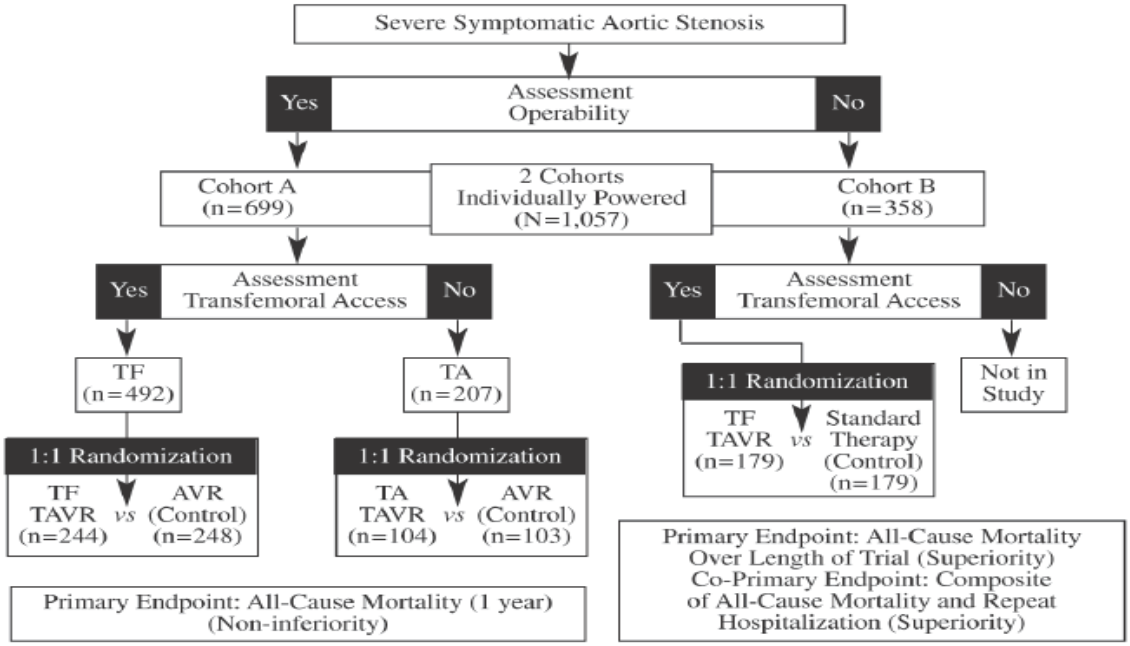
4.4 Device Modifications

During the pivotal trial, the design of the valve did not change; however, the delivery components continually evolved, but the changes made to the delivery system were minor.

FDA Comment: FDA has no concerns with the device modifications and believes that the clinical data collected in the PARTNER trial are applicable to the current design of the device and delivery system proposed in this PMA application.

5. THE PARTNER TRIAL– STUDY DESIGN

The PARTNER trial was a prospective, unblinded, randomized, controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV, via transfemoral or transapical (Cohort A only) delivery, in a stratified population of high risk (Cohort A) or inoperable (Cohort B) patients. Because the study enrolled two distinct populations, the two Cohorts were separately-powered and analyzed. As depicted in the diagram below, an initial stratification based on operability for aortic valve replacement (AVR) surgery was used to assign the patients to Cohort A or B. Assignment to Cohorts was followed by determination of vascular access for transfemoral delivery. Patients who were considered high surgical risk and eligible for transfemoral access were stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Cohort A patients who were not eligible for transfemoral access were evaluated as candidates for transapical delivery and, if appropriate, randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who were considered non-surgical candidates were stratified into Cohort B and randomized to treatment (transfemoral AVR) or control ("standard" therapy). Those assigned to Cohort B who did not meet the criteria for transfemoral delivery were not enrolled in the study because the sponsor declined to have a transapical arm in Cohort B.



AVR=aortic valve replacement, TA=transapical, TAVR=transcatheter aortic valve replacement, TF=transfemoral.

Figure 2 - PARTNER Trial Enrollment

A total of 1057 subjects were enrolled at 27 sites in the PARTNER study in the two arms – 699 patients in Cohort A (transfemoral or transapical insertion of the SAPIEN compared to surgical aortic valve replacement); 358 patients in Cohort B (transfemoral insertion of the SAPIEN versus "standard" therapy in an inoperable population). As mentioned above, the Cohort A and Cohort B studies were separately powered. The PMA under consideration by this Panel today contains data from only the Cohort A study; data from the Cohort B study were already considered by the Panel on July 20, 2011.

The protocol was fully approved in March 2009 (Version 3.2), a few months before enrollment in Cohort A was complete (August 2009). The CAP study was approved to allow enrollment of Cohort A subjects in a non-randomized protocol.

For this Cohort A study, the data extract for the original PMA submission was performed on February 19, 2011. FDA requested an updated dataset of events through September 21, 2011. The statistical analysis plan (SAP) included in Protocol Version 3.2 was finalized in March 2009. Revisions were made to the SAP through March 25, 2011, but the primary endpoint analysis remained unchanged. However, it should be noted that the SAP was finalized after enrollment of most of the subjects.

5.1 Patient Selection Process and Enrollment Criteria

The existing risk assessment tools, such as the Society of Thoracic Surgeons (STS) risk calculator, were deemed inadequate as a stand-alone mechanism for patient selection in the population; therefore, FDA encouraged the sponsor to incorporate a minimum of two

experienced surgeons and a cardiologist to make the initial high risk decision, taking into account risk factors not evaluated by the STS risk calculator. This decision was then peer reviewed on routine case review conference calls.

The full list is in the protocol and provided in the sponsor's panel pack. The major inclusion and exclusion criteria for the Cohort A study are summarized below.

5.1.1 Inclusion Criteria

The major inclusion criteria for patient entry into the study included the following:

1) Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area (AVA) of < 0.8 cm^2 (indexed EOA < 0.5 cm^2/m^2). (Qualifying AVA baseline measurement must be within 45 days prior to randomization).
2) Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
3) Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥10 can be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.

5.1.2 Exclusion Criteria

The major exclusion criteria for patient entry into the study included the following:

1) Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition).
2) Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
3) Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).
4) Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorlin syndrome
5) Need for emergency surgery for any reason.
6) Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
7) Patient has been offered surgery but has refused surgery.

8) Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

There was not a specific exclusion criterion for patients with critical aortic stenosis who had co-morbid conditions limiting the length or quality of their life. This was an abbreviated listing of the main inclusion and exclusion criteria; there were a total of 29 entrance criteria for the subjects in this study.

5.2 Primary Safety and Effectiveness Endpoint

The primary effectiveness and safety endpoint for Cohort A is freedom from all cause mortality at exactly day 365, analyzed in the ITT population.

The hypotheses for the primary endpoint are:

$$H_0 : S_T(T) - S_C(T) \le -0.075$$
$$H_A : S_T(T) - S_C(T) > -0.075$$

where $S_T(T)$ is the freedom from all cause mortality at exactly day 365 for treatment arm and $S_C(T)$ is that for control arm.

The test statistic is $\frac{\hat{S}_{(T)}(T) - \hat{S}_{(C)}(T) + 0.075}{\sqrt{\hat{V}[\hat{S}_{(T)}(T)] + \hat{V}[\hat{S}_{(C)}(T)]}}$, where $\hat{S}_{(T)}(T)$ and $\hat{S}_{(C)}(T)$ are the survival rates estimated by the Kaplan-Meier algorithm, and $\hat{V}[\hat{S}_{(T)}(T)]$ and $\hat{V}[\hat{S}_{(C)}(T)]$ are the variances estimated by Greenwood's formula. The null hypothesis will be rejected, and non-inferiority concluded, if the test statistic is greater than 1.645.

In addition to formal analysis of non-inferiority endpoints, the Kaplan-Meier (KM) curves will be presented for each group in the analysis, and a 95% two-sided confidence interval for the difference of the curves will be shown.

FDA Comment: Please note that the initial sample size calculation was based on the assumptions that: 1) 65% of the patients would have the transfemoral approach, 2) the transfemoral patients would have an improved 12 month mortality for the SAPIEN (25%) versus open AVR (30%), and 3) the two transapical groups would have the same mortality (35%). It is acknowledged that the 7.5% non-inferiority margin for this hypothesis may not result in "clinically equivalent" results even though the statistical hypothesis is met.

5.3 Secondary Safety and Effectiveness Endpoints

This section discusses the secondary safety and effectiveness endpoints presented by FDA and those presented by the Sponsor. Although the approved clinical protocol contains four pre-specified secondary endpoints, FDA believes that there are endpoints that are more clinically relevant. Both will be discussed in this Executive Summary.

5.3.1 FDA Secondary Endpoints

FDA believes that serious adverse event endpoints are clinically important, and should be considered in the context of the totality of data demonstrating safety and effectiveness of SAPIEN. Specifically the following adverse events occurring at 1 year will be presented in this memo:

- Deaths;
- Neurological Events;
- Aortic Regurgitation;
- Bleeding;
- Vascular Complications; and
- Atrial Fibrillation.

5.3.2 Sponsor Secondary Endpoints

The Sponsor selected the following pre-specified secondary endpoints on which to focus the results of their study:

- Time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within 1 year. The MACCE definition included:
  - Death
  - Myocardial infarction (MI)
  - Stroke
  - Renal failure
- Total hospital days from the index procedure to one year post procedure
- NYHA functional classification at 1 year
- Six minute walk test at 1 year

FDA Comment: FDA acknowledges that there are agreed upon secondary endpoints that were prespecified in the clinical protocol. However, as clinical trial design has evolved, and more information has been learned about patients receiving TAVR, FDA believes it is appropriate to consider additional, clinically relevant endpoints as part of the totality of the data to evaluate overall safety and effectiveness of this device.

Other secondary endpoints proposed by the sponsor included:

1) Separate analyses of the primary endpoint in the transapical and transfemoral groups.
2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year.
3) Freedom from MACCE at 30 days, 6 and 12 months. MACCE definition includes death, MI, stroke and renal failure.
4) Evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, severe paravalvular leak or migration) at 30 days, 6 and 12 months.

5) Length of index hospital stay (ITT).
6) Total hospital days from the index procedure to one year post procedure (ITT).
7) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months (ITT).
8) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA/EOA at 30 days, 6 and 12 months.

FDA Comment: In addition to the primary and secondary endpoints above, additional endpoints were analyzed (see Sponsor's Briefing Book). The FDA summary will focus on what the FDA believes are the key endpoints.

5.4 Other Adjunctive Analysis

In addition to the pre-specified primary endpoint at one year and several secondary endpoints evaluated at 30 days, 6 months, and/or 1 year, FDA is also interested in the longer-term data provided by the sponsor. As part of the additional adjunctive analyses, FDA will also present 2 year data for mortality and major adverse cardiac and cerebrovascular events and findings related to the CAP cohort.

5.5 Comparison of Results to Sample Size Estimation

In calculating the sample size needed for the study, it was assumed that 65% of the patients would have the transfemoral approach (actual 70.4%). It was further estimated that the transfemoral patients would have an improved 12-month mortality for the SAPIEN (25%) versus open AVR (30%). The study indicates a 12 month mortality of 22.24% for SAPIEN and 26.36% for open AVR on the transfemoral approach. It was assumed that for the transapical approach, the 12 month mortality would be 35% for both transapical TAVR and open AVR. The study indicates a 12 month mortality of 29.04% for transapical TAVR and 27.86% for open AVR.

5.6 Analysis Populations

The sponsor has analyzed the study results based on two populations: Intent-To-Treat (ITT) and As Treated (AT). There is also a third population, the valve implant population, consisting of those patients who received the valve. A summary of the patient population is provided in the table below.

Table 1 - Summary of Analysis Population (N=699 Total)

	Intent-to-Treat (ITT)	As Treated (AT)	Valve Implant
Treatment TAVR	n=348	n=344	n=326
Control AVR	n=351	n=313	n=311
Total	n=699	n=657	n=637

5.6.1 Intent-To-Treat Population

Of the 699 patients in the high risk, Cohort A, 348 were assigned to TAVR (SAPIEN) treatment group (244 of whom were implanted via the transfemoral route, and 104 of whom were

implanted via the transapical approach), 351 were randomized into the AVR (control) group (248 of whom were eligible for transfemoral and 103 of whom were eligible for transapical), forming the Intent To Treat (ITT) population defined as all randomized patients.

5.6.2 As Treated Population

The As Treated (AT) population was based on the treatment actually received. Therefore, the As Treated population is defined as follows:

- *AT SAPIEN*: This population consists of the Cohort A patients randomized to the treatment arm for whom the study valve implant procedure is begun, and the day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the time the study catheter is placed in the patient in the catheterization laboratory." Four patients did not have an attempt at the procedure (i.e. ITT=348; AT=344)

  If a treatment patient in Cohort A is assigned to the transfemoral approach, and it is determined during further access evaluation that the transapical approach is needed, that patient will be considered a transapical patient for as treated analyses of implant subgroups. This will not impact the combined Cohort A analysis.

- *AT Control*: This population consists of the Cohort A patients randomized to the Control arm for whom the valve implant procedure is begun. The day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the induction of general anesthesia for the open operation." A total of n=38 patients were to have received a control valve, but did not (i.e., ITT = 351; AT = 313)

5.6.3 Valve Implant Population

The valve implant population is defined as the subset of the As Treated population consisting of those patients (Treatment or Control) for whom the valve is implanted and remains in position.

Among the AT patients, 18 TAVR patients did not have the valve in position at the end of 1 year. Thus the valve implant population includes 326 patients in TAVR arm. Two AVR patients did not have the valve implanted.

FDA Comment: The sponsor proposed using the ITT population for the primary endpoint analysis, and either the ITT or the AT population for the secondary endpoints, whichever is appropriate. FDA believes that all three analysis populations have limitations because of trial conduct considerations that will be discussed. Hence, all of the analyses will be used for evaluating the safety and effectiveness of the SAPIEN THV.

6. PATIENT DEMOGRAPHICS and PATIENT SELECTION

6.1 Baseline Demographics

The table below summarizes the baseline demographics for each group.

Table 2 - Patient Baseline Demographics

Characteristic	TAVR (SAPIEN) N=348	AVR (Control) N=351	*P*-value
Age (yr), mean±SD	83.6±6.8	84.5±6.4	0.07
Male sex, n (%)	201/348 (57.8)	198/351 (56.4)	0.82
STS score[b], mean±SD	11.8±3.3	11.7±3.5	0.61
NYHA (New York Heart Association) class, n/total n (%):			0.79
II	20/348 (5.7)	21/349 (6.0)	
III or IV	328/348 (94.3)	328/349 (94.0)	
Coronary artery disease, n/total n (%)	260/347 (74.9)	266/346 (76.2)	0.66
Previous myocardial infarction, n/total n (%)	92/347 (26.5)	103/346 (29.8)	0.35
Previous intervention, n/total n/total n (%)			
CABG (coronary artery bypass grafting)	148/348 (42.5)	152/349 (43.6)	0.82
PCI (percutaneous coronary intervention)	116/346 (33.5)	110/348 (31.6)	0.63
Balloon aortic valvuloplasty	46/348 (13.2)	35/349 (10.0)	0.20
Cerebral vascular disease, n/total n (%)	96/327 (29.4)	87/325 (26.8)	0.49
Peripheral vascular disease, n/total n (%)	149/345 (43.2)	142/341 (41.6)	0.70
COPD (chronic obstructive pulmonary disease), n (%):			
Any	152/348 (43.7)	151/351 (43.0)	0.88
Oxygen-dependent	38/220 (17.3)	38/229 (16.6)	0.90
Creatinine >2 mg/dl (177 µmol/liter), n/total n (%) [&]	37/343 (10.8)	22/344 (6.4)	0.04
Atrial fibrillation, n/total n (%)	81/199 (40.7)	75/172 (43.6)	0.60
Permanent pacemaker, n/total n (%)	69/348 (19.8)	76/349 (21.8)	0.58
Pulmonary hypertension, n/total n (%)	125/295 (42.7)	111/302 (36.8)	0.15
Extensively calcified aorta, n (%)	2/348 (0.60)	4/351 (1.1)	0.69
Deleterious effects of chest-wall irradiation, n (%)	3/348 (0.9)	3/351 (0.9)	1.00
Chest-wall deformity, n (%)	0/348 (0.0)	1/351 (0.3)	1.00
Frailty**	46/295 (15.6)	53/301 (17.6)	0.58
Liver Disease, n/total n (%)	8/348 (2.3)	11/349 (3.2)	0.64
Echocardiographic findings			
Aortic valve area – cm^2	0.7±0.2	0.6±0.2	0.11
Mean aortic valve gradient – mm Hg	42.6±14.6	43.5±14.3	0.42
Mean LVEF - %	52.5±13.5	53.3±12.8	0.59
Moderate or severe MR – n/total n (%)[#]	66/337 (19.6)	71/338 (21.0)	0.70

** Frailty was determined by surgeons using prespecified criteria, but FDA is not aware of any validated scoring system for this parameter

[&] To convert creatinine to micromoles/liter, multiply by 88.4.

[#] Moderate to severe regurgitation was defined as regurgitation of grade 3+ or higher

[b] The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

Of note, is that approximately 43% of the patients had a prior CABG, 10-13% had a prior balloon aortic valvuloplasty, 20% had a pacemaker, and 41-43% of patients had atrial fibrillation. The majority of the patients had been hospitalized for aortic stenosis in the past.

6.2 Operative Risk

The STS score predicted 11.7% for the 30-day mortality for the average surgeon at the average hospital. The Kaplan Meier (KM) 30-day mortality for the As Treated surgery control was 8.0%. Therefore the observed/expected ratio for the surgeons in this trial was 0.68 – indicating much

better than average surgeons. The Sponsor was advised before the study started that we expected that their surgeons would have an Observed/Expected ratio of 0.5 because the average surgeon performs approximately 8 aortic valve operations per year.

6.3 Patient Selection

(a) Variations in patient selection

The screening log shows that only 27% of the patients screened were included in the study, and the ratio of the number of patients screened to those excluded varied among the sites, as described in the table below.

Table 3 - Screening Results

Site	Ratio Screen failure/total screened	%
01	36/266	**14%**
18	58/146	40%
20	84/191	44%
15	181/289	**63%**
09	251/403	62%

FDA Comment: FDA notes that screening and subsequent enrollment practices were not homogenous. The large variation between the ratios of those screened to those enrolled may represent different selection criteria among sites.

(b) Variations in site enrollment ratios of inoperable to high risk

There was a 3.4 fold variation in the enrollment ratio of transapical (TA) to transfemoral (TF), and a 4.3 fold variation in the ratio of "high risk" cohort A to "inoperable" Cohort B subjects between the sites, as depicted in the table below, which tabulates the ratios for the 6 highest enrolling sites.

Table 4 - Site Variability in Enrollment Ratios

Site Number	Cohort A Randomized TA Patients	Cohort A Randomized TF Patients	TA/TF Ratio	Cohort A Randomized PMA Patients	Cohort B Randomized PMA Patients	Cohort A/ Cohort B Ratio
01	40	55	0.73	95	21	4.52
02	25	72	0.35	97	33	2.94
04	22	25	0.88	47	45	1.04
08	29	38	0.76	67	43	1.56
09	23	29	0.79	52	21	2.48
10	24	92	0.26	116	36	3.22

FDA Comment: Enrollment practices related to identification of "inoperable" and "high risk" patients were not homogenous across sites. These data indicate that there may have been variable selection criteria for both deciding on inoperability and determining whether the femoral artery approach was appropriate.

7. PRIMARY SAFETY and EFFECTIVENESS ENDPOINT RESULTS

The following section focuses on an analysis of the primary safety and effectiveness endpoint which evaluates freedom from mortality at one year. There are also discussions of the sensitivity analysis of the ITT and AT populations, validity of the data pooling, gender analysis for the primary endpoint, and a review of the differences in mortality between the transfemoral and transapical groups.

7.1 Results of Primary Endpoint - Freedom from All Cause Mortality at One Year

At the end of 1 year, there were 84 (out of 348) and 89 (out of 351) deaths in the TAVR and AVR arm in the ITT population, respectively. The Kaplan-Meier estimates of the all cause mortality rate at 1 year are stated to be 24.27% and 26.80% for the TAVR (treatment) and AVR (control) arm, respectively. The survival difference (TAVR-AVR) was 0.0253, and the 95% one-sided lower confidence limit (CL) for the difference was -0.0299, which is greater than the pre-defined non-inferiority margin (-0.075). The p-value for the non-inferiority test is 0.0014, indicating that the primary endpoint is met with a 0.075 non-inferiority margin.

In addition to the one year data, the Sponsor has also provided patient outcomes at 2 years, allowing FDA an opportunity to evaluate the longer-term results of SAPIN THV implantation. The (Kaplan-Meier) cumulative incidence curve for the all cause mortality to 24 months is shown below for the ITT population.

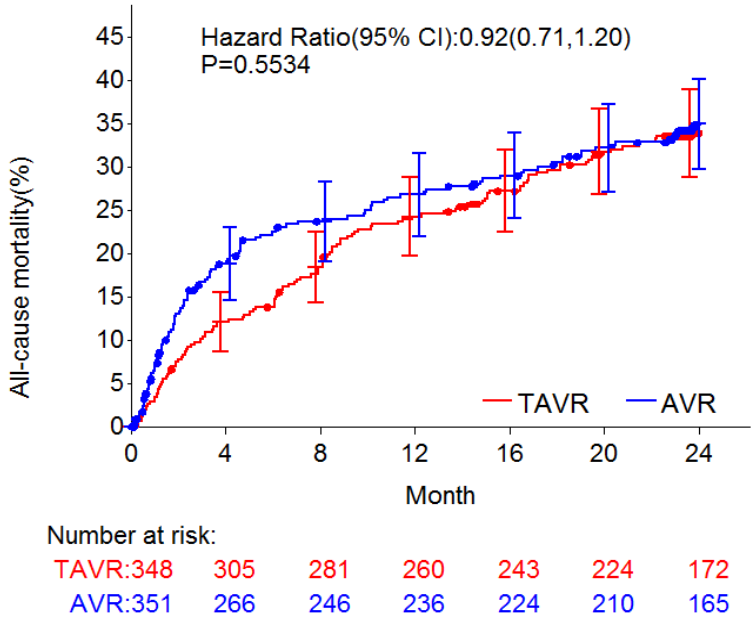


Figure 3 - Kaplan-Meier Cumulative Indidence Curve for All-Cause Mortality (ITT Population)

FDA comment: Based upon these data, there is no significant difference in mortality between the treatment and control groups at the 1 year endpoint. A careful review of the death narratives for this study did not raise any specific concerns regarding the causes of death in this study. However, the issue of AVR patients not receiving AVR, TAVR patients receiving AVR, and AVR patients undergoing concomitant operations makes evaluation of these endpoint results difficult. We note that there are limited data beyond 2 years from the PARTNER trial and the

long-term mortality comparison between SAPIEN THV and open surgery remains unclear. Therefore, the FDA believes that continued long-term follow-up is warranted in a Post-Approval Study (PAS) should this device be approved. FDA will be seeking Panel input on specific endpoints for the PAS.

7.2 Sensitivity Analyses for ITT Population

The Sponsor performed worst case analysis to assess the robustness of the mortality results. The assumption used in the worst case analysis was that AVR patients who were censored prior to 1 year were considered alive at 1 year, and AVR patients who did not receive the procedure were also considered alive at 1 year; and that TAVR patients who were censored prior to 1 year were considered dead as of the censoring date, and TAVR patients who did not receive the procedure were also considered dead at 1 year.

The primary endpoint of all cause mortality is still met with a 0.075 non-inferiority margin on the worst case analysis.

FDA Comment: Although the primary endpoint was met, issues related to potential selection bias confound the interpretation of these results.

7.3 Analysis of AT Population

For the AT population, at the end of 1 year, there are 81 (out of 344) and 78 (out of 313) deaths in the TAVR and AVR arm, respectively. The Kaplan-Meier estimates of the all cause mortality rate at 1 year are stated to be 23.7% and 25.2% for the TAVR (treatment) and AVR (control) arm, respectively. The survival difference (TAVR-AVR) was -1.5, and the 95% one-sided lower CL for the difference was -0.004, which is greater than the pre-defined non-inferiority margin of -7.5%. The p-value for the non-inferiority test is 0.0037, indicating that the primary endpoint is met with a 7.5% non-inferiority margin on the AT population.

FDA comment: Issues of potential selection bias that confound interpretation of the AT primary endpoint include the following: 1) the exclusion in the AT analysis of 10% of patients who did not receive AVR and the inclusion in the AT analysis of the 11 patients in the TAVR arm who received AVR; 2) inclusion of the two patients in the AVR arm who received TAVR; and 3) the issue of concomitant operations in the AVR arm.

These confounding factors must be considered in the overall interpretation of these data.

7.4 Site Poolability for the Primary Endpoint

Center effect on the primary endpoint was evaluated by the sponsor using Cox regression. Using Site 01 as the reference group, hazard ratios of different sites over the reference group were reported for ITT population and for AT population. Except for one center (Site 15), all other 95% CI of center hazard ratios include 1. Site 15 contributes 25/699 = 3.58% of the ITT subjects in the database and 20/657=3.0% of the AT subjects.

A logistic regression model containing treatment, site, and treatment by site interaction is performed on all cause mortality as well as on MACCE. No significant interaction is detected on either endpoint (p-value > 0.15).

FDA Comment: Although the study was not powered to detect differences in treatment effect between sites with or without a significant financial interest, FDA conducted a descriptive analysis of all cause mortality and MACCE using the data provided in the PMA. There did not appear to be a treatment effect observed between sites with or without a significant financial interest.

7.5 Gender Differences for Primary Endpoint

In ITT population, males compose 57.8% (201/348) of TAVR arm and 56.7% (198/351) of AVR. In AT population, males are 57.6% (198/344) of TAVR arm and 57.2% (179/313) of AVR.

In both ITT and AT populations, males perform better on AVR. All-cause mortality was numerically higher in the TAVR arm than that in the AVR arm. The mortality rates at 1 year are 28.52% and 25.21% for TAVR and AVR, respectively, in the ITT population. The mortality rates at 1 year are 27.44% and 22.67% for TAVR and AVR, respectively, in the AT population. The 95% one-sided lower confidence limits of survival difference (TAVR-AVR) are -10.69% and -12.14% for ITT and AT, respectively. Both are less than the pre-specified non-inferiority margin (-7.5%). Non-inferiority was NOT met in the male stratum.

In both ITT and AT populations, females perform better on TAVR. All-cause mortality was numerically higher in the AVR arm than that in the TAVR arm. The mortality rates at 1 year are 18.45% and 29.03% for TAVR and AVR, respectively, in the ITT population. The mortality rates at 1 year are 18.58% and 28.56% for TAVR and AVR, respectively, in the AT population. The 95% one-sided lower confidence limits of survival difference (TAVR-AVR) are 2.36% and 1.64% for ITT and AT, respectively. Both are greater than the pre-specified non-inferiority margin (-7.5%).). Non-inferiority was met in the female stratum.

In addition, for the all cause mortality, it is found that there exists significant interaction between treatment and gender on both ITT (p-value = 0.0495) and AT (p-value = 0.0387) populations in a CoxPH regression model with gender, treatment and gender*treatment.

In the continued access protocol (CAP) cohort, 1588 patients were enrolled in the TAVR registry (since randomization was eliminated for the CAP cohort) and 770 of them are female (48.5%). At one year, the K-M estimated event rates in ITT population are 18.54% for females and 25.94% for males, respectively. Those numbers are numerically close to those observed in the randomized study (18.45% and 28.52%, respectively).

FDA Comment: Although this study was not powered on each gender separately, as indicated above, a *post hoc* analysis is performed. The non-inferiority was met in the female stratum, but not in the male stratum. In addition, there exists qualitative interaction in gender and treatment (i.e. treatment effects are in the opposite direction for males and females). The panel will be asked to consider the totality of the data by considering the gender data from both the IDE

pivotal and the CAP cohort in making a final assessment of the safety and effectiveness in this patient population.

7.6 Transfemoral and Transapical Approaches

Though the interaction of treatment and approach (transfemoral versus transapical) is tested and is found to be not significant (p-value > 0.15), it is of interest to perform separate analyses of the primary endpoint in the transapical and transfemoral groups.

The separate analyses of the primary endpoint in the transapical and transfemoral groups are of interest and are presented here for both the ITT and AT groups.

7.6.1 Transfemoral Approach

In the ITT population, for the transfemoral approach, there were 244 patients and 248 patients in the treatment and control groups, respectively. For the all cause mortality, the KM event rates at 1 year are 22.24% and 26.36% for the transfemoral treatment group and control group, respectively. The survival difference is 4.12% (Transfemoral-control). The 95% one-sided lower CL for the survival difference is -2.34%.

In the AT population, for the transfemoral approach, there are 240 patients and 221 patients in the treatment and control groups, respectively. For the all cause mortality, the KM event rates at 1 year are 21.35% and 25.18% for the transfemoral treatment group and control group, respectively. The survival difference is 3.83% (transfemoral-control). The 95% one-sided lower CL for the difference is -2.68%.

7.6.2 Transapical Approach

In the ITT population, for the transapical approach, there were 104 patients and 103 patients in the treatment and control group, respectively. For the all cause mortality, the KM event rates at 1 year are 29.04% and 27.86% for the transapical treatment group and control group, respectively. The survival difference is -1.18% (transapical-control). The 95% one-sided lower CL for the difference is –11.69%.

In the AT population, for the transapical approach, there are 104 patients and 92 patients in the treatment and control group, respectively. For the all cause mortality, the KM event rates at 1 year are 29.07% and 25.28% for the transapical treatment group and control group, respectively. The survival difference is -3.79% (transapical-control). The 95% one-sided lower CL for the difference is -14.29%.

FDA Comment: The mortality rates are numerically higher in the treatment group for the transapical approach. FDA seeks Panel input on whether the device should be approved for both transfemoral and transapical implantation based on the data provided.

Because the number of transapical patients are limited in the IDE randomized clinical trial (RCT), the panel will also be asked to consider the totality of the data by considering the RCT

transapical and CAP transapical patients in making a final assessment of the safety and effectiveness in this high risk, operable (Cohort A) population.

8. PATIENT TREATMENT

The following section highlights FDA's interpretation of data related to patient treatment.

8.1 Heterogeneity of Treatment

This trial was designed to compare isolated AVR to TAVR. However, a review of the data resulted in a comparison that includes a heterogeneous group of patients and a combination of therapies as shown in the figure below.

CONTROL		TREATMENT
• AVR • AVR + concomitant operations • No AVR – no intervention • Delayed AVR • TAVR	VS.	• TAVR • Attempted TAVR then AVR • No TAVR - nothing • TAVR – no intervention for concomitant conditions

Figure 4 - Heterogeneity of Treatment

FDA Comment: Due to the heterogeneity of treatment control group, interpretability of any differences between patient groups is limited. The following sections more fully described the following:

1. Failure to attempt to treat;
2. Delay in treatment; and
3. Concomitant operations.

8.2 Failure to Attempt to Treat

(a) Imbalance in Failure to Attempt to Treat

There was an imbalance between the control and treatment groups as to those patients who refused/withdrew (28 fold increase in AVR group), patients who died before the procedure (2.3 fold increase in AVR group), and those judged to have deteriorated (5 fold increase in AVR group). The table below demonstrates the issue of differential numbers of failure to treat.

Table 5 – Reasons for Failure to Treat

Reason	TAVR (N=348)	AVR (N=351)
Died before the procedure	2 (0.6%)	5 (1.4%)
Refusal	1 (0.3%)	17 (4.8%)
Withdrawal	0 (0%)	11 (3.1%)
Pre-treatment deterioration	1 (0.3%)	5 (1.4%)
Total	4 (1.1%)	38 (10.8%)

Only 3/28 of the patients who refused AVR or withdrew from the study were known to be dead at one year (one patient refused AVR because she "started feeling better").

FDA Comment: It cannot be assumed that the "sickness" of the patients who chose to withdraw from the study was the same as those who were treated. If less sick patients differentially withdrew from the AVR arm, this could possibly bias results towards the treatment group in an Intent-to-Treat analysis. The imbalance between reasons for failing to treat patients has the potential of introducing selection bias in both the ITT and As Treated (AT) analyses.

This phenomenon of failure to treat in the control group occurred differently at various sites, as is shown in the table below.

Table 6 - Percentage of Randomized Control Patients Not Receiving AVR (Sites enrolling >25 control patients)

Site	**10**	**02**	**08**	**04**	**15**
Total control pts enrolled at site	116	97	67	47	25
# control pts not getting AVR	1	5	6	5	5
% pts not getting control AVR	1%	5.1%	9.0%	10.6%	20%

Almost 11% of the patients did not get the assigned treatment in the AVR group.

FDA Comment: Because these patients had critical aortic stenosis, it was expected that they would be treated per the group to which they were assigned and be indicated for isolated valve replacement. The trial results are confounded as a result of failing to treat these patients, possibly indicating a biased result towards worse outcomes in the ITT AVR group, because some patients did not receive the recommended treatment for their disease and the issue of concomitant operations in the AVR group. This could also bias results of the As Treated analysis against the AVR group if those patients not treated were "less sick" and therefore were excluded from the As Treated analysis, or if those patients had concomitant operations. These data need to be interpreted carefully since patient treatment across sites was not homogenous due to the large variation in the rates of Failure to Treat among sites.

(b) Imbalance in Failed Treatment

In the TAVR group, a total of n=18 SAPIEN patients were excluded because either the SAPIEN was never implanted or did not remain *in situ* at the end of the index procedure, as detailed in the following table.

Table 7 – Reasons for Unsuccessful TAVR

Reasons for Unsuccessful TAVR	Status	n
Valve embolization	Did not remain *in situ*	5
TEE findings	Not implanted	5
Access problems	Not implanted	4
Died prior to valve deployment	Not implanted	2
Femoral artery tear	Not implanted	1
Large sigmoid septum	Not implanted	1
Total		18

In the control AVR group two patients were operated on but did not receive a valve. One patient had a severely calcified aorta and subsequently underwent TAVR (alive at one year) and another was a reoperation who died during the procedure.

FDA Comment: There is an imbalance in patients who had attempted treatment that did not result in an implanted valve. Similar to earlier comments, the impact of these events on overall data interpretability is unknown.

(c) Cross-Over - Use of AVR in TAVR arm

There were a total of 11 AVR procedures performed in patients randomized to TAVR, several of which were emergency procedures. These patients are summarized below:

i. Not implanted because of congenital septal condition
ii. Annulus 26mm, converted to AVR
iii. Annulus >25mm, converted to AVR done
iv. SAPIEN embolized to LV, emergency AVR (multiple complications)
v. SAPIEN embolized to LV, emergency AVR (multiple complications)
vi. SAPIEN embolized to LV, emergency AVR (multiple complications)
vii. Annulus 27mm, converted to AVR done
viii. SAPIEN embolized to LV, emergency AVR (patient died)
ix. SAPIEN embolized to descending aorta, emergency AVR (multiple complications)
x. Aortic dissection during attempted TAVR, AVR 3 mos later
xi. abandoned due to access procedures, AVR 3 mos later

FDA Comment: These patients were included in TAVR arm for both the ITT and AT analyses. The impact of these patients on the overall results is unknown since the beneficial effects of AVR could possibly introduce bias in favor of the TAVR arm. FDA also notes that in the TAVR arm, these patients would have remained untreated for their critical aortic stenosis without the use of open AVR as a bailout procedure. It should also be noted that converting a patient from an elective TAVR to an emergency AVR is known to increase the risk of mortality.

8.2.1 Delay in Treatment

In the TAVR group, there was a mean 11-day delay from randomization to the procedure, whereas in the AVR group the mean delay was 16 days. The data also show that more patients in the control group had a considerable delay between randomization and treatment than in the treatment group. For instance, Pt # [redacted] did not have AVR because of "worsening lab values" – however, this occurred 14 months after randomization.

FDA Comment: The impact of delay in treatment on results is difficult to interpret, but could have confounding effects on the assessment of overall safety and effectiveness.

8.2.2 Concomitant Operations in the AVR group

This trial was intended to compare isolated open AVR to isolated TAVR. The inclusion/exclusion criteria specifically excluded patients from the study with "Untreated coronary artery disease (CAD) requiring revascularization." However, 21 patients (6.7%) of the AVR group had a concomitant coronary artery bypass (CAB) procedure. Patients with CAD remained untreated in the SAPIEN group.

In addition, multiple exclusion criteria were intended to exclude the need for operation for associated conditions. However, concomitant operations for associated conditions were performed in 13.1% (41/313 AT) of the control patients. These data are provided in the table below.

Table 8 - Concomitant Operations

CABG	20
CABG + aortic endarterectomy	1
MV repair	4
MV replacement	1
MV repair, annular enlargement	1
MV repair, root enlargement	1
TV repair	1
TV annuloplasty, Root replacement	1
Root/arch replacement	3
Aortoplasty	2
Ascending Aortic endarterectomy	3
Ablation for afib	1
Excision Left Atrial Appendage	1
TOTAL Patients with concomitant operations (% total 40/313) (As Treated)	40 (12.8%)

Of the 40 patients who underwent concomitant operations in the control group, 42.5% (17/40) had died by 1 year.

FDA Comment: The operative risk of combination operations (AVR+CAB, AVR+ other valves, ablation, etc.) is known to be higher than for isolated valve procedures. This higher operative

risk could bias safety results in a short-term study. Patients randomized to the SAPIEN group who were untreated for these concomitant conditions could affect long-term results for TAVR, but might not be captured in this shorter term study. This could introduce bias in favor of the treatment group in both the ITT and AT analyses because of the short-term increased risk of concomitant operations and because the long-term effectiveness of treating these conditions were not captured by the short-term (1 year) primary effectiveness endpoint.

8.2.3 Lack of Standardized Antithrombotic Treatment in the AVR population

There were no pre-specified antithrombotic regimens in the control group in the protocol for this study. The following regimen for antithrombotic drugs was provided for the TAVR arm.

Table 9 - Recommended Medication Regimen

Medication	Pre-Procedure	During Catheterization	Post-Procedure	30-Day Follow-up	6 month follow-up
IV Heparin	PRN	5000 IU bolus, then as needed to achieve/maintain ACT ≥250 sec			
Aspirin	75-100 mg QD		75-100 mg QD	75-100 mg QD	75-100 mg QD
Clopidogrel*	300 mg (if not on long-term therapy)	75 mg QD	75 mg QD	75 mg QD for 6 months	

* Ticlopidine could be used instead of clopidogrel at the investigator's discretion

The non-protocolized antithrombotic regimen resulted in important variations between the two arms of the trial, especially in the use of clopidogrel in the larger transfemoral arm. The following table presents the actual antithrombotic use over the first year.

Table 10 - Actual Medication Regimen

Medication	**Randomized Patients (% pts)**				
		Transapical		**Transfemoral**	
	Visit	**AVR (N=103)**	**SAPIEN (N=104)**	**AVR (N=248)**	**SAPIEN (N=244)**
Aspirin	Baseline	64/103 (62.1%)	64/104 (61.5%)	150/248 (60.5%)	166/244 (68.0%)
	1 yr	52/103 (50.5%)	62/104 (59.6%)	143/248 (57.7%)	171/244 (70.1%)
Clopidogrel	Baseline	29/103 (28.2%)	25/104 (24.0%)	42/248 (17.0%)	52/244 (21.3%)
	1 yr	19/103 (18.4%)	22/104 (21.2%)	26/248 (10.5%)	72/244 (29.5%)
Warfarin	Baseline	21/103 (20.4%)	19/104 (18.3%)	50/248 (20.2%)	49/244 (20.1%)
	1 yr	8/103 (7.8%)	11/104 (10.6%)	17/248 (6.9%)	28/244 (11.5%)

FDA Comment: The lack of a standardized antithrombotic protocol in the AVR arm makes evaluation of the post-procedural stroke rate difficult to interpret. FDA recognizes there are currently no approved antithrombotics labeled for TAVR.

9. ADDITIONAL SECONDARY ENDPOINTS

9.1 FDA Clinically Important Endpoints

9.1.1 Serious Adverse Events

The following table summarizes the Serious Adverse Events (SAEs) that occurred in this study during the 30 day post-operative period, 31 days to 1 year, overall events from 0 day-1 year, and events occurring beyond 1 year:

Table 11 - Serious Adverse Events (AT Population)

Outcome	30 Days		31 Days – 1 Year		0 Days – 1 Year		> 1 Year	
	Pooled TAVR (N=344)	Pooled AVR (N=313)	Pooled TAVR (N=325)	Pooled AVR (N=284)	Pooled TAVR (N=344)	Pooled AVR (N=313)	Pooled TAVR (N=259)	Pooled AVR (N=229)
Death	18(5.2%)	25(8.0%	63(19.4%)	53(18.7%	81(23.5%)	78(24.9%)	49(18.9%)	42(18.3%)
All Stroke	15(4.4%)	8(2.6%)	4(1.2%)	1(0.4%)	19(5.5%)	9(2.9%)	4(1.5%)	8(3.5%)
Myocardial Infarction	0(0.0%)	1(0.3%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)	2(0.8%)	5(2.2%)
Major Vascular Complication	38(11.0%)	12(3.8%)	0(0.0%)	0(0.0%)	38(11.0%)	12(3.8%)	1(0.4%)	0(0.0%)
Renal Failure	13(3.8%)	14(4.5%)	4(1.2%)	5(1.8%)	17(4.9%)	19(6.1%)	2(0.8%)	0(0.0%)
Major Bleeding (CEC)	37(10.8%)	72(23.0%)	20(6.2%)	14(4.9%)	52(15.1%)	84(26.8%)	11(4.2%)	12(5.2%)
New Atrial Fibrillation	30/321 (9.3%)	57/290 (19.7%)	14/254 (5.5%)	3/190 (1.6%)	44/326 (13.5%)	60/294 (20.4%)	N/A	N/A
New Pacemaker	16(4.7%	14(4.5%)	4(1.2)	2(0.7%)	20(5.8%)	16(5.1%)	2(0.8%)	3(1.3%)
Presence of Mild or greater (>1+) aortic insufficiency	229/334 (68.6%)	53/287 (18.5%)	174/268 (64.9%)	36/197 (18.3%)	250/336 (74.4%)	64/293 (21.8%)	47/97 (48.5%)	9/77 (11.7%)

A more detailed review of some of these events is discussed in the next sections.

9.1.2 Deaths

Table 12 - Death Event Rates by Implant Approach in Treatment and Control Group (ITT Population)

Implant Approach	Study Arm	Number of Patients Who Died at 12 months
Transfemoral	TAVR (N=244)	54
	Open AVR (N=248)	62
Transapical	TAVR (N=104)	30
	Open AVR (N=103)	27
Pooled	TAVR (N=348)	84
	Open AVR (N=351)	89

FDA Comment: Evaluation of these results must take into consideration the trial conduct issues such as the 10% of patients not getting AVR, the inclusion of the 11 patients in the TAVR arm who received AVR, and the confounding issue of concomitant operations in 13% of the AVR arm.

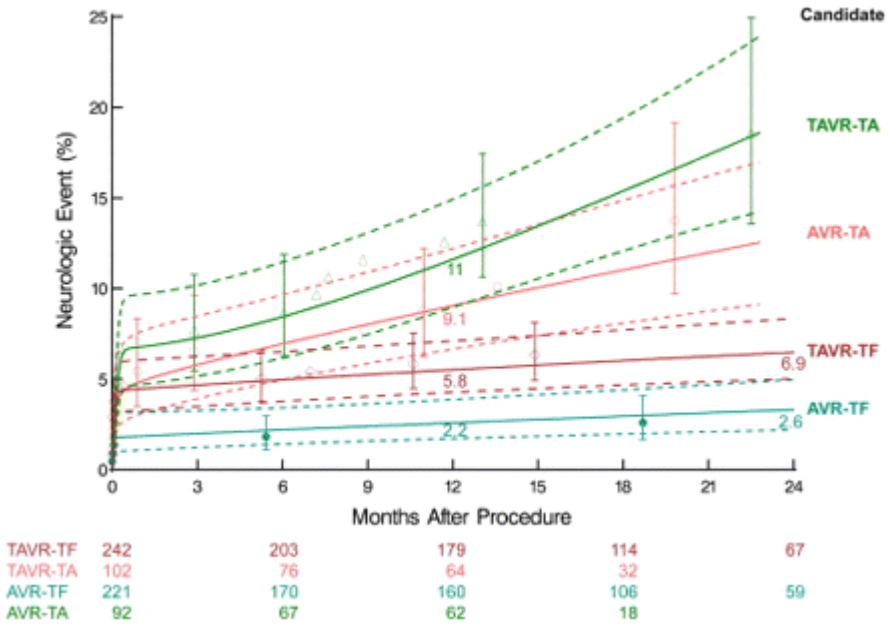
FDA acknowledges the mortality increase in patients undergoing transapical delivery of SAPIEN THV and is requesting panel input on the risk/benefit considerations of the transapical approach in these patients.

9.1.3 Neurological Events

The agreed upon, pre-specified definition of stroke was as follows:

> A stroke is a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.

FDA considers the rate of neurological events to be analyzed based upon this definition and requested that the sponsor present the data using the agreed upon definitions of stroke and transient ischemic attacks (TIA), which are included in the graph below taken from a publication (Miller et al. 2012) by the trial investigators:



Likelihood of neurologic event when the competing risk of death is taken into consideration in each of the 4 treatment subgroups. Depicted in light blue is the curve for the likelihood of a neurologic event after aortic valve replacement (AVR) in the TF stratum (AVR-TF), the salmon-colored curve is that for AVR patients assigned to the TA stratum (AVR-TA), the brown curve is for the transfemoral transcatheter aortic valve replacement patients in the TF stratum (TAVR-TF), and the green curve is for the TAVR patients in the transapical stratum (TAVR-TA). Number of patients at risk is denoted below the horizontal axis at 6-month intervals. [Miller, et al. J Thorac Cardiovasc Surg 2012;143:832-43]

Figure 5 - Likelihood of Neurologic Events for Different Treatment Subgroups

FDA comment: Comparing open AVR and SAPIEN, there is a doubling of the neurological event rate in the SAPIEN patients in the acute periprocedural period (0-30 days). FDA also notes that the transapical patients had higher neurological events rates than transfemoral delivery in both groups. For the transfemoral arm, it appears that the TAVR and AVR curves are parallel after the acute period, thus indicating no difference in stroke rates chronically. However, with the transapical approach, there appears to be both an increased early stroke rate and an increased stroke rate chronically. Neurological adverse events remain an important safety consideration for this device, and should be weighed in the overall determination of safety and effectiveness

for the SAPIEN device.

The cause of neurological injury with transcatheter valve implantation is multifactorial. One important consideration is management of antithrombotics. The PARTNER trial did not require patients to be on a protocolized antithrombotic regimen. In light of this, as well as the increased neurological event risk discussed above, the sponsor has proposed a protocolized anticoagulation/antiplatelet regimen to be used in the proposed post-approval study. While this may aid in reducing the neurological event risk for patients receiving the SAPIEN, other risk mitigation measures may also need to be taken into account.

Five published studies[10- 14] comparing cerebral imaging pre- and post-implantation in transcatheter aortic valve implantation patients showed cerebral infarction rates of 73%, 84%, 68%, 91%, and 68%. The identification of stroke in the current study depended on recognition of symptoms by the cardiovascular team. Because of the elevated neurological event rate in this study and with consideration of the papers mentioned above, future FDA-regulated studies of transcatheter valve implantation will require more intense neurological evaluations. FDA plans to seek panel input on how to interpret the benefit to risk profile in this high risk group of patients who suffer more neurological events but appear to gain no mortality benefit compared to the AVR group.

9.1.4 Aortic Regurgitation

The table below presents the total amount of aortic regurgitation (mild or greater, and moderate or greater) reported from the core laboratory at the listed follow-up time points in both arms. Note that these totals include all sources of regurgitation, including both central regurgitation and paravalvular leak.

Table 13 - Mild, Moderate or Severe Total Aortic Regurgitation (% Patients)

Pooled	30day	6 month	1 yr
AVR	16.5	14.3	139
SAPIEN	62.2	60.2	55.8

Table 14 - Moderate or Severe Aortic Regurgitation (% Patients)

Pooled	DC	30day	6 month	1 yr	2 yr
AVR	1.2	1.7	1.1	2.5	1.3
SAPIEN	10.2	14.8	14.8	9.3	8.2

The following figure shows the correlation between aortic insufficiency and death in the present study.

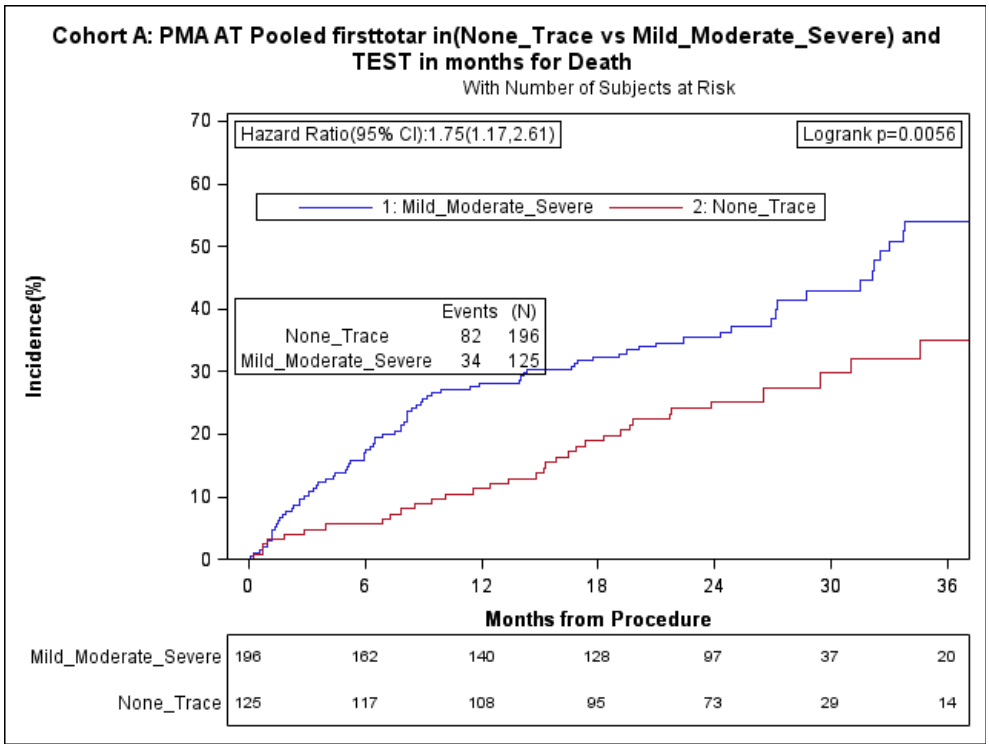


Figure 6 -Mortality Risk of Mild/Moderate/Severe Perivalvular Leak in TAVR Patients

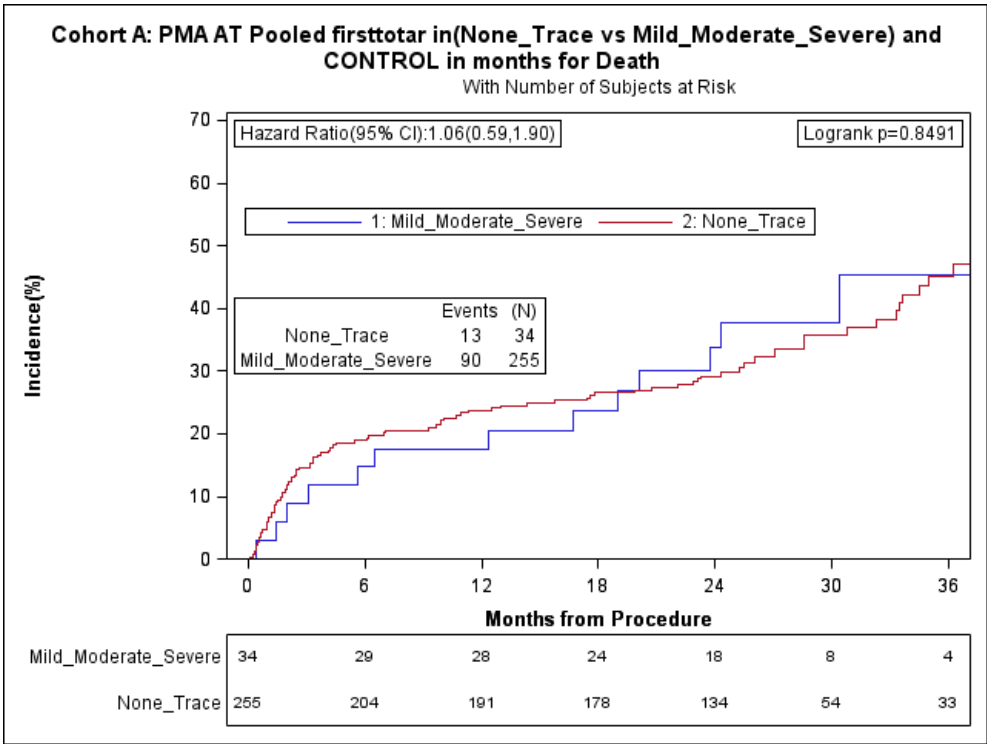


Figure 7 - Mortality Risk of Mild/Moderate/Severe Perivalvular Leak in Control AVR Patients

FDA comment: Mounting evidence[15-17], including the data from this trial, demonstrates an association between aortic regurgitation and mortality in patients who receive TAVR. These data also show that the amount of AR is appreciable and does not decrease over time in the SAPIEN group. (This association was not demonstrated in the patients receiving AVR; however, the number of patients with moderate/severe AR in the control AVR group was very small and is inadequate to draw any conclusions.)

FDA was interested in a comparison of the Sponsor's grading of AR to the American Heart Association (AHA)/American College Cardiology (ACC) classification of AR that was relevant at the time the trial was initiated, however, FDA was not provided that information.

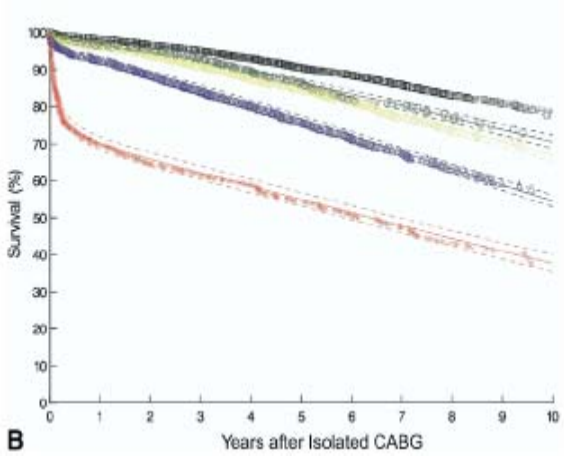
The Sponsor hypothesizes that the difference in mortality between TAVR patients with no/trace AR and those with mild/moderate/severe AR is due to differences in baseline characteristics in this randomized study. The FDA does not view that there is support for this hypothesis. FDA recognizes that the study was not powered to detect differences between the AVR and TAVR with regard to AR, however, there may be a relationship between these factors. Based on the available data, aortic regurgitation in the TAVR patient population appears to impact long-term survival. The amount of AR and its clinical significance over time in the SAPIEN group remains a concern and will need to be monitored in the potential post-approval setting if the device is approved.

9.1.5 Bleeding

The PARTNER protocol prospectively defined adverse events relating to bleeding and vascular complications as:

Any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g., vision loss) or necessitates transfusion of greater than 3 units PRBCs or pericardiocentesis procedure. The complication *bleeding event* applies to all patients whether or not they are taking antithrombotic drugs, since bleeding events can occur in patients who are not receiving antithrombotics. Embolic stroke complicated by bleeding is classified as a neurologic event under *embolism* and is not included as a separate bleeding event. Hemorrhage that requires 2 or more units of transfusion within the index procedure shall be reported as serious adverse events. Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection. Events reported as major or minor bleeding and hemorrhagic events are differentiated by whether they require intervention.

The graph below shows that most of the mortality associated with blood transfusions occurs in the first year after transfusion.[18]



(Transfusion in Coronary Artery Bypass Grafting is Associated with Reduced Long-Term Survival)
(Black, no blood transfusion; green, 1 unit; yellow, 2 units; blue 3–5 units; and red ≥6 units of red blood cells transfused; CABG = coronary artery bypass grafting; PRBC = perioperative red blood cell.)
Figure 8 - Mortality (as It Relates to Blood Transfusions)

The site variability for the complication of Major Bleeding is high.

Table 15 - Site Variability in Maor Bleeding in Control AVR (Sites with >20 control cases)

Site #	%controls with Major Bleeding
01	32
02	21
03	30
08	43
09	12
10	13

FDA Comment: Since blood transfusions are a marker for mortality, they are important to track. In the present study that has a primary endpoint of mortality at one year, the major effect of blood transfusion on mortality is captured within the primary endpoint. However, the site 3.5 fold variability in blood transfusion is dramatic and indicates that blood conservation techniques at many of the sites may not have been optimal. This represents an area for improvement in the surgical treatment of aortic valve disease.

9.1.6 Vascular Complications

The PARTNER protocol prospectively defined adverse events relating to vascular complications as follows:

Aortic Dissection:
Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention.

Hemorrhagic Vascular Complication:
Vascular complications include the following:

1) Hematoma at access site >5 cm
2) False aneurysm
3) Arterio-venous fistula
4) Retroperitoneal bleeding
5) Peripheral ischemia/nerve injury
6) Any transfusion required will be reported as a vascular complication unless for a clinical indication clearly other than catheterization complication.
7) Vascular surgical repair

From the table below, vascular injury was present in 5.4% (17/313) of AVR patients and 17.7% (61/344) of the SAPIEN patients in the AT analysis.

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Table 16 – Vascular Complications in the AT Population

Vascular Complication	TA-AVR	TA-TAVR	TF-AVR	TF-TAVR
Hematoma at access site >5cm	1	0	2	12
False aneurysm	0	1	2	4
Arterio-venous fistula	0	0	0	2
Retroperitoneal bleeding	0	0	1	4
Peripheral ischemia/nerve injury	0	0	0	0
Vascular Surgical Repair	6	4	5	34
Total	7	5	10	56

It appears that 19% of the SAPIEN patients had serious adverse events relating to the access procedure. The table below, which FDA created, based on a review of the CEC narratives that adjudicated "Vascular Complication" (with possible/probable/definite relation to the device or the procedure) lists the most serious of the vascular complications.

Table 17 - Vascular Complication Types in the AT Population

Vascular Complication in SAPIEN (CEC adjudicated)	**#events**
Myocardial perforation	3
VSD	1
Thoracic aortic dissection	3
Abdominal aortic dissection	1
Iliac or Ileofemoral artery dissection	16
Femoral artery dissection	11
Iliac artery perforation	6
Femoral artery perforation	6
Femoral pseudoaneurysm	6
Iliac or femoral artery embolus	7
Femoral or retroperitoneal hematoma	16
AV fistula	2
Total Events	**78**
# patients with Vascular Complication	**64**
Total patients	**344**
% patients with vascular complication	**18.6%**

FDA Comment: The study results indicated that 19% of the SAPIEN patients had serious adverse events relating to the access procedure. These injuries most often resulted in the need for prosthetic material and/or graft repair of the injuries. These patients remain at risk of graft thrombosis and infection throughout the remainder of their lives, a long-term risk that should be closely monitored in the post-approval setting if this device is approved. In an effort to address this risk, the sponsor has proposed a comprehensive training program for new practitioners. Compliance with this program, as well as an assessment of its effectiveness, will be important parameters in a potential post-approval study.

9.1.7 Atrial Fibrillation (AF)

For AF, data on new onset of AF were provided but this was not analyzed according to the presence of AF at each time period. Prior to the start of the study, we assumed that this endpoint was measuring the creation of long-term AF. However, this turned out to be an erroneous assumption. Short (e.g. minutes) events of AF were counted the same as the permanent or persistent atrial fibrillation for the sponsor's "new onset AF" endpoint.

FDA requested data on the occurrence of AF at the 6 month and one year follow-up visits, which is provided below:

Table 18 - Patients with No AF at Baseline Who Developed AF at Scheduled Follow-Up Exam (AT Population, n = not censored as of 6 months or 1 year visit)

	AVR %	SAPIEN %	Relative Risk SAPIEN/AVR	Missing Data AVR %	Missing Data SAPIEN %
6 month visit (Control n=162, SAPIEN n=208)	7/162 (4.3%)	12/208 (5.8%)	1.35	51/162 (31.5%)	45/208 (21.6%)
1 year visit (Control n=155, SAPIEN n=185)	4/155 (2.6%)	14/185 (7.6%)	2.92	59/155 (38.1%)	41/233 (17.6%)

Table 19 - Patients with AF at Baseline Who Did Not Have AG at Scheduled Follow-Up Exam (AT Population, n = not censored as of 6 months or 1 year visit)

	AVR %	SAPIEN %	Relative Risk SAPIEN/AVR	Missing Data AVR %	Missing Data SAPIEN %
6 month visit (Control n=54, SAPIEN n=65)	19/54 (35.1%)	12/65 (18.5%)	0.53	19/54 (35.2%)	11/65 (16.9%)
1 year visit (Control n=49, SAPIEN n=55)	15/49 (30.6%)	13/55 (23.6%)	0.77	16/49 (32.6%)	5/55 (9.1%)

FDA comment: There is a higher incidence of transient AF (the sponsor's definition of "new onset" atrial fibrillation in the open AVR group, which counts short events, e.g. a few minutes, hours or days), but these data do not indicate how many patients are in atrial fibrillation at each follow-up visit. Other than hospital stay, there are no proven chronic consequences of transient postoperative atrial fibrillation.

When AF is captured at the chronic visits, it was numerically more likely that control patients who had AF at entrance into the study would be out of AF after open AVR than those patients in the SAPIEN group. Also, it was numerically more likely that patients without AF at baseline treated with the SAPIEN would develop AF at the chronic follow-up examinations. The interpretation of this analysis is limited by the trial conduct issues of failure to get the randomized treatment, the non-specific method of classifying AF, the concomitant operations, and the large amount of missing data.

9.2 Other Endpoints

9.2.1 Endocarditis

There were 5 cases of endocarditis in the AVR and 5 cases in the TAVR patients.

FDA Comment: This confirms the need for longer-term (>1-2 years) monitoring of this device in these patient groups, as the patients are at risk over the life of the transcatheter valve, as are open AVR patients.

9.2.2 Device Malfunctions

Device malfunction was experienced in 5 patients. Four of five malfunctions were due to the delivery system. The fifth event was a case where two of the leaflets were not functioning after implantation, and this patient died.

FDA Comment: FDA has no concerns regarding the data provided for device malfunction. FDA continues to emphasize the need for appropriate training and labeling to mitigate risks

associated with device malfunction. The panel will be asked to comment on the training and labeling for this device.

9.2.3 Other Serious Adverse Events

Data were also collected for the following important adverse events: myocardial infarction, renal failure (chronic dialysis for >30 days), renal insufficiency (creatinine >3.5), bradyarrhythmic event, and mitral valve compromise. There is no difference between arms in these complications.

FDA Comment: FDA has no concerns with regard to these data.

9.2.4 Device Success/Procedure Success

Device success is evaluated on Valve Implant Population. Device success was defined as successful delivery and deployment of the device and retrieval of the delivery catheter resulting in an aortic valve area greater than 0.9cm^2 with < 3+ aortic regurgitation in the earliest evaluable echocardiogram (which may not be the same echocardiogram for both parameters) and only one valve is implanted in the correct anatomical position. In the TAVR group, 17.2% (56/326) of the valve implant population did not have device success and 1.23% (4/326) can not be evaluated. This does not count the 18 patients who had the procedure attempted but in whom the valve did not remain *in situ*. The reasons for these 18 cases of no device success are listed in the following table:

Table 20 - Device failure

Reason for No Device Success	# of Patients
Aortic Regurgitation >2+	34
Aortic Valve Area ≤0.9cm^2	13
More than 1 TAVR used	7
Two or more of above	2
Not implanted or not *in situ* at end of procedure	18

Procedure success is evaluated on Valve Implant Population. Procedure success was defined as Device Success + no 30-day MACCE. Out of 326 patients, 25% (n=82) of the patients did not have Procedure Success. The reasons for lack of procedure success were no Device Success in 55 patients and MACCE in 27 patients.

These data show that 100 out of 344 (29%) TAVR patients who had the procedure attempted (AT population) either failed to have the valve implanted, failed to have Device Success, or failed to have Procedure Success.

FDA Comment: The table above is based on the sponsor's definition of AR >2+. However, the FDA prospectively defined a lack of success as AR > 1+. FDA requested this information, but it was not provided for review.

9.2.5 Quality of Life

At 30 days, there was a statistically significant difference, in favor of SAPIEN. At 1 year, there is no clinically important difference in any of the sub-components of the KCCQ.

FDA comment: FDA cautions interpretation of these results in the setting of an unblinded trial, particularly in a comparison of patients undergoing open heart surgery versus patients receiving TAVR.

9.2.6 Follow-Up Time

The mean follow-up time for the primary endpoint is 1.6 ±1.0 years for the pooled AVR and 1.8±1.0 years for TAVR. The Sponsor has provided additional data out to 2 years for certain endpoints.

FDA Comment: FDA believes that this is insufficient follow-up to assess durability of the device in patients who are expected to live longer than 2 years. The Panel is asked to recommend a method of assessing durability in the long-term.

9.2.7 Days from Randomization to Procedure

In the TAVR group, there was a mean 11 day delay (median 7 days) from randomization to the procedure, whereas in the AVR group the mean was 16 days (median 9 days).

FDA Comment: Because of the number of covariates, there is no statistical way to conclusively interpret these results. However, based on FDA's clinical interpretation, substantial delays between randomization and the procedure could have resulted in clinical status changes in the patients.

9.2.8 Procedure Data

The following table provides data on the procedures for patients in Cohort A. These data demonstrate that the SAPIEN procedure took, on average, over 4 hours and required general anesthesia in all patients. It is difficult to interpret the control AVR data since 13% of these patients had concomitant operations, such as other valve replacements, CABG, atrial fibrillation ablation, etc.

Table 21 - Procedure Data

Measured variable	TAVR (N=344)		AVR (N=313)
	Transapical (N=104)	Transfemoral (N=240)	
Total time in Cath Lab or OR in minutes (mean [min-max])	224.9 (93-595)	242.8 (0-624)	323.7 (0-750)
Skin to skin time in minutes (mean [min-max])	110 (9-514)	141 (32-510)	230.0 (169-295)
Fluoroscopy time in minutes (mean [min-max])	14 (5-60)	30 (7-121)	0 (0-0)
Volume of contrast in mL (mean [min-max])	104 (0-275)	148 (15-507)	0 (0-0)
Use of cannulation for cardiopulmonary bypass (n[%])	9/102 (8.8%)	5/234 (2.1%)	313/313 (100%)
Use of general anesthesia (n[%])	102/102 (100%)	240/240 (100%)	309/309 (100%)
# of devices used			
0 [n(%)]	3/102 (2.9%)	11/238 (4.6%)	N/A
1 [n(%)]	91/102 (89.2%)	216/238 (90.8%)	313/313 (100%)
2 [n(%)]	7/102 (6.9%)	10/238 (4.2%)	N/A
3 [n(%)]	1/102 (1.0%)	1/238 (0.4%)	N/A
More than one valve used [n(%)]	3/104 (2.9%)	4/240 (1.7%)	N/A
Emergent operation due to device or procedure failure [n(%)]	1/104 (1.0%)	3/240 (1.3%)	12/313 (3.8%)
Valve size			
19 mm [n(%)]	N/A	N/A	37/312 (11.9%)
21 mm [n(%)]	N/A	N/A	124/312 (39.7%)
22 mm [n(%)]	N/A	N/A	1/312 (0.3%)
23 mm [n(%)]	52/101 (51.5%)	109/233 (46.8%)	109/312 (34.9%)
25 mm [n(%)]	N/A	N/A	37/312 (11.9%)
26 mm [n(%)]	49/101 (48.5%)	124/233 (53.3%)	N/A
27 mm [n(%)]	N/A	N/A	3/312 (1.0%)
29 mm [n(%)]	N/A	N/A	1/312 (0.3%)
Adverse event during procedure [n(%)]	20/102 (19.6%)	51/240 (21.3%)	46/313 (14.7%)

FDA Comment: Results of interest are that all patients in the TAVR and AVR arms required general anesthesia. The total time in the procedure room was an hour less for TAVR patients than AVR patients, but this includes patients with concomitant operations. Fluoroscopy time averaged 30-35 minutes, with a maximum time of over 2 hours, but no radiation dose data were collected in this study. (In future studies these will be collected.)

9.2.9 Cardiac Remodeling

The following parameters represent the echocardiographic markers for cardiac remodeling.

Table 22 - Echocardiographic Markers of Cardiac Remodeling

Parameter	Time	Pooled Control mean	Pooled SAPIEN mean
EF	Baseline	53.34	52.60
	1 yr	57.00	56.58
	delta	**+3.66**	**+3.98**
LVED vol	Baseline	119.05	123.34
	1 yr	102.10	114.15
	delta	**-16.95**	**-9.19**
LVES vol	Baseline	58.37	63.02
	1 yr	45.42	52.87
	delta	**-12.95**	**-10.15**
LV mass	Baseline	278.20	282.37
	1 yr	233.50	250.28
	delta	**-44.70**	**-32.09**

FDA Comment: The parameters presented in the table above were chosen because of the association with remodeling. There appears to be a slight numerical trend towards better LV remodeling with open AVR, but these differences are not clinically significant.

9.2.10 Aortic Valve Area

FDA Comment: FDA has no concerns regarding these data. No patients had aortic stenosis on follow-up echocardiogram.

9.2.11 Surgical Access for AVR and TAVR

FDA asked the sponsor to provide information regarding the nature of the incisions used for open AVR and whether the patients were redo operations. The following information was provided:

Table 23 - Prior Cardiac Surgery Stratified by Procedural Approach in AVR Patients (AT Population)

	Prior Open Heart Surgery (including CABG)		
	No	Yes	Total
AVR Full Sternotomy	128 (48.7%)	135 (51.3%)	263 (84.3%)
AVR Minimal Incision	45 (91.8%)	4 (8.2%)	49 (15.7%)
Total	173 (55.5%)	139 (44.6%)	312 (100.0%)

Frequency Missing = 1

FDA Comment: This indicates that about third of the first-time surgical patients had minimally invasive approaches and that about three quarters of the TAVR patients required an open operation. This is important information for patients to know when they are weighing their options and the risk/benefit considerations between open AVR and possible catheter-based implantation.

FDA asked for information regarding MACCE events in the control group (AT) broken down into whether the patients had a previous CABG. Interestingly, those with first time operations had higher rates of early (relative risk (RR) =2.1) and late (RR=1.5) death. Early (<30d) complications of stroke were higher (RR=2.2) in the redo group, but the late incidence of stroke was higher in the non-redo group. FDA does not have additional data to interpret if these results are independent of the procedure approach (full sternotomy versus minimal incision).

FDA also asked the sponsor to provide information regarding how many patients needed an incision for direct arterial access as opposed to a percutaneous puncture for arterial access. The following information was provided:

Table 24 - Arterial Access for TAVR Procedures

Access Procedure	N (%)
Percutaneous catheter puncture only	66 (27.5%)
Incision for direct access Or Vascular operation after percutaneous access	171 (71.25%)
Missing information	3 (1.25%)

FDA comment: This trial was promoted as a trial comparing open operation for valve replacement with transcatheter aortic valve replacement (AVR versus TAVR). It is clear from these data that only about a quarter of the patients had only a transcatheter insertion of the SAPIEN THV. Therefore, this trial was a comparison of open surgical transthoracic AVR with open surgical transthoracic or open peripheral vascular transcatheter valve placement.

9.2.12 Explants

There were no explants in the AVR group. One Cohort A patient underwent surgical excision of the SAPIEN aortic bioprosthesis due to fungal endocarditis and underwent open AVR a year after SAPIEN placement.

9.2.13 More Than One Valve Used

Seven patients underwent what the Sponsor labeled as procedures with more than one valve used in the Cohort A study. A brief description of these cases is included here:

i. Deployed in SAPIEN secondary to severe AI (patient died 10 days later)
ii. Deployed in SAPIEN secondary to severe AI
iii. Deployed in descending annulus after first valve in descending aorta
iv. Deployed in SAPIEN secondary to severe AI and 2 leaflets not working
v. First valve in descending aorta, second in "proper" position (Type B dissection)
vi. Hemodynamic collapse after first valve, second deployed.
vii. First valve in descending aorta, second in annulus

FDA comment: FDA is concerned that if the SAPIEN becomes commercially available, widespread use of the valve-in-valve technique for previously surgically inserted bioprosthetic valves might occur. While the valve-in-valve implant method was utilized rarely in the SAPIEN IDE trial, there are many reports in the literature regarding the use of this technique in Europe. In addition, no preclinical testing has been conducted to support the safety of this procedure. This is significant given the potential for corrosion (fretting and galvanic) as well as other unknown risks associated with valve-in-valve implantation, such as long-term durability, valve migration/embolization, and access to the coronary ostia. Without any pre-clinical testing, and based on the limited clinical data available, it is difficult to draw conclusions regarding the short- and long-term safety of valve-in-valve implantation. Several risk mitigation measures, such as labeling, training, or requirements for additional testing may be appropriate in order to address this concern.

9.3 Sponsor Identified Secondary Endpoints

As noted earlier, there were four pre-specified secondary endpoints associated with mathematical hypotheses. These data are presented in this section.

9.3.1 Major Adverse Cardiac and Cerebrovascular Events (MACCE) – Time from randomization to the first occurrence of a MACCE within 1 year

For the purposes of this analysis, MACCE includes all-cause death, myocardial infarction (MI), all stroke, and renal failure. The KM event rates at 1 year are 26.6% and 27.4% for TAVR and AVR respectively for the AT population. The event rate difference (TAVR-AVR) is -0.8% with a two-sided 90% C.I. of (-6.6%, 4.9%).

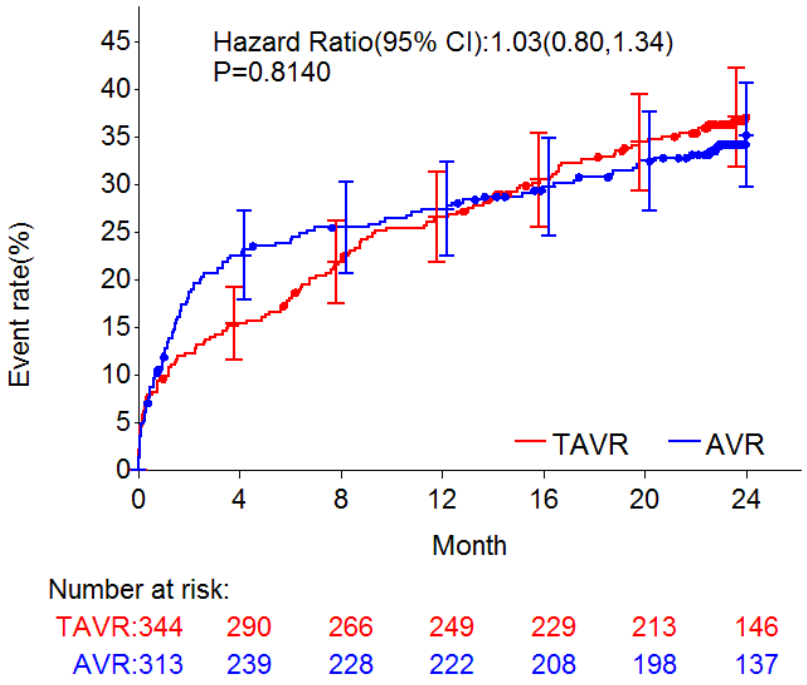

Figure 9 - First Occurrence of MACCE (AT Population)

Table 25 - MACCE Event at One Year in AT Population (using pre-specified adverse event definitions)

	Patients in group	Events	Patients with Event	KM Event rate at 1 Year
Death				
AVR	313	78	78	25.2%
TAVR	344	81	81	23.7%
Myocardial Infarction				
AVR	313	1	1	0.3%
TAVR	344	0	0	0.0%
Renal Failure				
AVR	313	11	10	3.5%
TAVR	344	7	7	2.1%
All Stroke				
AVR	313	9	9	3.0%
TAVR	344	19	19	5.8%
MACCE				
AVR	313	99	85	27.4%
TAVR	344	107	91	26.6%

FDA Comment: The aforementioned concerns related to other analyses raised regarding trial conduct must also be considered in this analysis and interpretation of MACCE. Since the MACCE composite is not hierarchically weighted, it is important to examine each component adverse event, in particular, the almost 2-fold increase in the stroke rate. In addition, the definition of MACCE in this study does not include the important serious adverse events of vascular injury, hemorrhage, and aortic insufficiency.

9.3.2 Total Hospital Days to One Year Post-Procedure

In the ITT population, the mean number of hospital days through 1 year was 16.32 ± 18.0 days for the treatment group and 18.75 ± 22.58 days for the control. The median hospital stay days are 10 and 13 days for TAVR and AVR, respectively.

FDA Comment: This analysis of hospital days is difficult to interpret because of the same trial conduct issues raised throughout this document; especially that of the concomitant operations performed in the AVR group. The overall impact of potential study bias needs to be incorporated into the safety and effectiveness assessment for this device.

9.3.3 New York Heart Association (NYHA) Class at One Year

For the endpoint of NYHA functional classification at 1 year, by treating NYHA as continuous variable, it is found that the mean of NYHA was 1.70 ± 0.77 for the SAPIEN group and 1.7 ± 0.76 for the control (ITT population).

The most important observation is that the above analysis is done by including only in-window visit values, deleting all death (no imputation) and any missing for reasons other than death. Specifically, there are 251 patients in the test arm and 226 patients in the control arm included in the analysis.

There was a statistically significant difference in NYHA at 30 days, in favor of SAPIEN. Improvements of NYHA (as compared to baseline) at one year are shown in the following two tables for TAVR and AVR, respectively.

Table 26 - Cross Tabulation of NYHA Comparing Baseline and 1 Year in TAVR Patents (AT Population)

NYHA	1 Year						
Baseline	Class I	Class II	Class III	Class IV	Died	Missing	Total
Class I	0	0	0	0	0	0	0
Class II	7	4	1	0	6	2	20
Class III	54	43	12	1	29	5	144
Class IV	58	46	19	4	45	8	180
Died	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0
Total	119	93	32	5	80	15	344

Table 27 - Cross Tabulation of NYHA Comparing Baseline and 1 Year in AVR Patients (AT Population)

NYHA	1 Year						
Baseline	Class I	Class II	Class III	Class IV	Died	Missing	Total
Class I	0	0	0	0	0	0	0
Class II	6	3	2	0	3	2	16
Class III	47	42	9	1	30	5	134
Class IV	50	46	10	4	44	9	163
Died	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0
Total	103	91	21	5	77	16	313

FDA Comment: Although the sponsor conducted multiple sensitivity analyses to assess the impact of missing data, the fact that such a significant amount of the data were missing makes it impossible to draw any firm conclusions regarding these results. FDA believes that the differences between the groups are clinically insignificant and does not have any concerns with regard to these data. However, FDA wishes to note that there was a noticeable amount of missing data and plans to ask the Panel to comment on the impact of missing data on the overall interpretation of the results. Furthermore, these data must also be carefully considered in the context of an unblinded trial.

9.3.4 9.3.4 Six Minute Walk Test (6MWT)

The 6 Minute Walk endpoint was added to the protocol after this unblinded study had started enrollment. Based on the available data from the test performed at 1 year, SAPIEN patients walked 164.96 ± 128.4 meters and control patients walked 69.84 ± 134.4 meters. Specifically, there are 198 patients in the test arm and 150 patients in the control arm included in the analysis.

The most important observation is that the above analysis is performed by including only in-window visit values, deleting all death (no imputation) and any missing for reasons other than death.

FDA comment: Although the sponsor conducted multiple sensitivity analyses to assess the impact of missing data, the fact that such a significant amount of the data were missing makes it impossible to draw any firm conclusions regarding these results. FDA has concerns about the persistent limitation at one year for the 6 minute walk and the minimal availability of paired data for functional assessments. The setting of an unblinded trial further complicates the ability to draw conclusions from these data.

10. CONTINUED ACCESS STUDY COHORT – ADDITIONAL IDE TRIAL DATA

The non-randomized Continued Access Cohort (NRCA) study enrolled 843 transapical patients and 745 transfemoral patients. The following table shows that no patient has two events, so the numbers of patients with events and the number of events are the same.

Table 28 - All Cause Mortality - Randomized TAVR and NRCA Patients by Implant Approach (ITT Population)

		≤ 30 Days			31 Days – 1 Year		
	Patients in Group	Events	Patients with Event	KM Event rate at 30 Days	Events	Patients with Event	KM Event rate at 1 Year
Death							
NRCA - TA	843	57	57	7.0%	93	93	24.1%
Randomized TAVR - TA	104	4	4	3.8%	26	26	29.0%
NRCA - TF	745	24	24	3.3%	83	83	20.6%
Randomized TAVR - TF	244	8	8	3.3%	46	46	22.2%

Table 29 -Stroke - Randomized TAVR and NRCA Patients by Implant Approach (ITT Population)

		≤ 30 Days			31 Days – 1 Year		
	Patients in Group	Events	Patients with Event	KM Event rate at 30 Days	Events	Patients with Event	KM Event rate at 1 Year
Stroke							
NRCA –TA	843	17	16	2.0%	6	6	3.7%
Randomized TAVR – TA	104	6	6	5.8%	3	3	9.6%
NRCA TF3.7%	745	29	28	3.9%	10	10	5.8%
Randomized13.3% TAVR 5.8%- TF	244	10	10	4.1%	1	1	4.6%

FDA Comment: These data appear to demonstrate improved or consistent results when compared to the randomized trial results. The stroke rate in the CAP cohort appears to have decreased. Although the reasons for this are not clear, it could be related to this being a different patient population since the CAP is a non-randomized single arm registry. Other reasons could be the learning curve effect or different thresholds for stroke identification. The Panel will be asked to comment on the CAP results, particularly as they apply to the TA patients.

11. EUROPEAN CLINICAL EXPERIENCE

The PARTNER EU trial (130 patients), and all of the registries in Europe (SOURCE Registries, n=3382), used the EuroScore risk prediction system as defining high risk and inoperability (i.e., predicted mortality >50%).

FDA Comment: The EuroScore was developed primarily using data from coronary bypass patients with a relatively small contribution from isolated aortic and mitral valve patients. Several studies have compared the validated STS Risk predictor score for aortic valve replacements with the EuroScore in the aortic stenosis population and have found the EuroScore to be invalid, noting that the EuroScore can over predict risk by three (or more) times the actual risk. As a result, the trial results in Europe are very difficult to interpret because it is unclear who the patients were and who were enrolled in these registries. For example, surgeon input as to operability was not required in these trials. Other significant limitations include the lack of a concurrent control or availability of longer-term follow-up.

Therefore, the European experience cannot answer critical clinical questions regarding longer-term durability and outcomes. It is for this reason that FDA will require a major US post-approval registry designed to assess, among other things, longer-term results and generalizability of IDE trial results to new centers if this device is approved.

12. FDA PERSPECTIVES AND ISSUES

The PARTNER trial met the pre-specified criteria for study success, as defined by the primary safety and effectiveness endpoint of all-cause mortality throughout the duration of the study, demonstrating non-inferiority of the SAPIEN THV as compared to the Control group. Throughout the Sponsor's Executive Summary/Briefing Book, statements are made for various complications, such as stroke, that "no statistical differences were observed." These analyses were not pre-specified and/or did not have alpha allocated, and therefore, any p-values associated with these analyses should be interpreted with caution. When evaluating whether the results of the trial support the safety and effectiveness of the SAPIEN THV for the proposed indications, the following points should be considered.

12.1 Long-Term Durability

This is a study of a permanent device used to treat a chronic disease in a population with an expected survival of many years. The patients in this study were followed for 2 years but there is limited longer-term data to assess valve durability.

12.2 Patient Treatment

The results of this study show that the comparison was not between "open" AVR and percutaneous AVR. For patients having open AVR who had not had a previous operation, about one half of the patients had a minimally invasive approach. For TAVR patients, about three quarters required either an open surgical procedure for direct arterial access, or an open surgical procedure for vascular repair after a percutaneous approach. Therefore, this trial compared open AVR with transcatheter AVR that frequently required surgery for vascular access or repair.

12.3 Trial Conduct

There are a variety of trial conduct factors that could have introduced bias or could have confounded the analysis. These factors make interpretation of this non-inferiority trial challenging.

a. There was a large imbalance between groups (more in the AVR group) as to those who refused/withdrew, died before the procedure, or judged to have deteriorated. This has the potential to introduce a selection bias. There was a large variation between sites in these categories.

b. In the control group, concomitant operations (e.g. ablation, mitral and tricuspid operations, etc.) were performed in 13.1% of the control patients. The complete treatment of associated conditions would be expected to result in increased safety events in the short-term (1 year), but would provide benefit over not treating these conditions in the long term. In fact, 40% of the patients with concomitant operations were dead at the one year endpoint. This would tend to bias this short term trial in favor of the test device.

c. There is a very large variation in the proportion of patients screened and enrolled at each institution and a substantial difference between the percentages of patients assigned to High Risk vs Inoperable in this trial. This suggests a differing patient population among centers and possible different criteria for evaluating inoperability.

d. Although the SAPIEN arm had a recommended antithrombotic regimen, no such protocol was specified in the control AVR arm.

e. Thirty percent of the overall patient enrollment was by investigators who had a financial conflict of interest. The study was not powered to detect a difference in treatment effect between sites with or without a significant financial interest.

12.4 Safety

There were increased rates of important adverse events in the SAPIEN THV treatment group.

a. **Neurological Rate** - There was a doubling of the neurological event risk in the SAPIEN arm compared with AVR in the periprocedural period and an increased rate in the transapical SAPIEN arm. Neurological adverse events remain an important safety consideration for this device and impact the overall risk-benefit profile of the SAPIEN THV.

b. **Vascular Complications** - There is about a tripling of vascular injury in the SAPIEN group which may have long-term consequences since patency of prosthetic grafts is a safety issue for the long-term. The AVR group had a much higher incidence of blood transfusions, which is associated with increased mortality, especially in the first year.

c. **Atrial Fibrillation** - There is a higher incidence of "new onset" atrial fibrillation in the open AVR group, but this simply counts short events (e.g. a few minutes, hours or days) as the incidence and does not tell us how many have persistent/permanent atrial fibrillation. Other than hospital stay, there are no proven chronic consequences of transient postoperative atrial fibrillation. When one looks at the incidence of atrial fibrillation at 6 months and 1 year post-procedure, there is no appreciable difference between the two groups. It is surprising that only one AVR patient had ablation as a concomitant procedure. In the future, it is expected that lower risk patients would have more ablations.

12.5 Device Implantation and Delivery - Transapical versus Transfemoral and Valve-In-Valve

a. There appears to be a substantially higher complication rate with the transapical procedure such that the clinical non-inferiority to open AVR is questionable based on the results of this PMA comparison. The study was not powered to address safety in either transfemoral or transapical alone.

b. There appears to be an important trend toward decreased survival in male patients undergoing transapical procedures.

c. While the valve-in-valve implant method was utilized rarely in the SAPIEN IDE trial, there are many reports in the literature regarding the use of this technique elsewhere. No preclinical testing has been conducted to support the safety of this procedure. This is significant given the potential for corrosion (fretting and galvanic) as well as other unknown risks associated with valve-in-valve implantation, such as long-term durability, valve migration/embolization, and access to the coronary ostia.

12.6 Informed Consent Process

Ensuring that patients have true informed consent for this new technology is important. A comparison of the rates of adverse events important to patients needs to be presented. Such events would include death, strokes, vascular complications, the long-term effects of aortic insufficiency, and bleeding, as well as the incisions needed for access.

12.7 Other Considerations

a. There are no clinically important differences in days alive out of hospital over the year, NYHA, or 6MWT at one year. The evaluation of NYHA and 6MWT are limited because a significant amount of the data were missing, which makes it impossible to draw any firm conclusions.

b. While all Cohort A patients have been followed to at least 2 years, there are relatively few patients with longer-term follow-up. The feasibility studies and studies done outside of the U.S. have longer-term follow-up, but the comparability of these patients to those in the PARTNER trial is unknown. While not impacting the primary hypothesis testing for the PARTNER trial, the limited longer-term data available for

this novel device and procedure supports the need for robust post-approval follow-up to bolster our understanding of device durability and longer-term performance if the device is approved.

13. POST APPROVAL STUDY

The sponsor has proposed to conduct two post-approval studies if this PMA is approved. The first study proposes long-term follow-up of the patients remaining in the premarket cohort (referred to as the "Extended Follow-up of Premarket Cohort Study"). For the second study, the sponsor proposes a non-randomized, prospective, consecutively enrolled registry of new high risk patients undergoing transcatheter heart valve replacement therapy with the SAPIEN THV (referred to as the "New Enrollment Study").

13.1 Rationale

The considerations for whether a post-approval study is needed include the following:

1. Information may be needed regarding longer-term performance of the device.
2. Performance of the device in the community may differ from that in the premarket studies, and may vary by patient population and by device user,
3. Effectiveness of training programs may require monitoring of learning curve.
4. More information on specific sub-groups from the premarket studies may be needed.
5. Monitoring of adverse events (namely procedural vascular complications) and real world experience may be needed.

13.1.1 Longer Term Performance

The current study was designed to follow the patient's status for one year, and, during this time frame, all-cause mortality was lower in the transcatheter aortic valve replacement (TAVR) arm compared to the surgical aortic valve replacement (AVR) arm. However, the difference in all-cause mortality between the two study arms was not significant at 1 year. By 2 years, the hazard ratio for all-cause mortality between the two study arms was 0.92 (95% CI = 0.71, 1.20). At 6-months, quality of life varied between the two study arms in favor of the AVR patients. However, by one year this difference dissipated. In order to assess the long-term safety and effectiveness of the device beyond the pre-specified 1-year study duration, the premarket patients should be followed for at least 5 years through the continuation of the premarket study –the earliest mechanism by which long term performance safety signals in a population for which the device is used as indicated among trained and experienced operators may be identified.

13.1.2 Community

The PAS should include patients who reflect real-world use. As the device is available postmarket, physicians may feel free to use TAVR in patients for whom surgical AVR is more appropriately indicated.

13.1.3 Training Programs

As the device increases in availability among hospitals, the procedure itself may pose a risk to the patients due to the operator's deficit in training and experience. In order to reduce the risk of procedure related adverse events and monitor a potential learning curve in a broader patient and provider population, a training program needs to be instituted within the PAS.

13.1.4 Subgroups

Less than 10% of patients in the premarket study were from a minority population. Minorities, such as Blacks and Latinos, are traditionally at an increased risk of cardiovascular morbidity and mortality. In a study by Taylor, et al.[19], after adjusting for clinical baseline values, Black race was associated with an increased risk of prolonged ventilation, postoperative stay >14 days, and reoperation for bleeding after AVR. Therefore, the population in the premarket study may not accurately reflect the real-world population who share a need for the device and for whom outcomes may differ. Though the PAS will be designed as a registry (all-comers), the sponsor will be asked to perform subgroup analyses by race.

13.1.5 Adverse Events

Based on premarket data, adverse events of interest include, but are not limited to, strokes, procedural and post procedural vascular bleeding, and a composite endpoint of MACCE event or repeat surgery for valve failure or major vascular complication.

13.2 POST APPROVAL STUDY I: Extended Follow-up of Premarket Cohort Study

Objective
The objective is to determine long-term safety and effectiveness of the device and delivery systems (transfemoral and transapical), including evaluation of device durability and patient quality of life in high risk surgical patients with symptomatic severe aortic stenosis.

Hypothesis
No hypothesis testing was proposed.

Data Collection (endpoints)
For long term data collection at the 2 through 5 year visits, additional analysis of echo data will be conducted for the purpose of studying durability. No new data collection is needed. There is also collection and analysis of QOL data at the 2 through 5 year visits, for the purpose of studying long term performance of patients.

Sample Size
All patients currently enrolled within the IDE study.

Statistical Plan
This evaluation will primarily be based on descriptive statistics. Comparison of the QoL values to baseline data will be made using t-tests. For the echo data, a linear model will be fit to actual data only, beginning with the 30-day visit.

13.3 POST APPROVAL STUDY II: New Enrollment Study

Objective
The objective the non-randomized, prospective, consecutively enrolled registry study is to assess short-term and long-term evaluation of newly enrolled patients compared with premarket cohort; adherence to indications for use (learning curve); differences in patient populations and outcomes (i.e., safety, including stroke); device durability; and patient quality of life in high risk patients.

Hypotheses
The primary hypotheses involve comparisons of:

- A VARC safety composite endpoint at 30 days post-procedure (all-cause mortality, disabling stroke, life-threatening (or disabling) bleeding, peri-procedural MI, acute kidney injury - Stage 3, repeat procedure for valve-related dysfunction); and
- An effectiveness composite endpoint at 1 year post-procedure to newly developed objective performance criteria (all-cause mortality, change in NYHA, mean ICU and total index procedure hospital length of stay).

Data Collection (endpoints)
Patients will undergo clinical follow-up at discharge, 30 days and 1 year as well as follow-up data collection with CMS linkage to TVT national registry at 2 years, 3 years, 4 years and 5 years. The two primary endpoints with testable hypotheses are stroke at 30 days (4.65%) and 1 year (5.81 %) for the pooled approaches. Endpoints will also be stratified by the transapical and transfemoral approach.

Sample Size
Enrollment will consist of a minimum of 700 Transfemoral patients and a minimum of 1010 Transapical patients.

Statistical Plan
The VARC composite and stroke endpoints will be estimated via Kaplan-Meier with 95% confidence intervals. Secondary endpoints will be assessed using descriptive statistics, with no formal hypothesis tests.

FDA comment: It is not clear whether the composite primary endpoint should include all strokes, rather than only "disabling" strokes as captured in the proposed post-approval study. The New Enrollment Study provides an opportunity to further evaluate the learning curve by specifically comparing the results of the first patients treated by a newly trained interventionist to later patients of the same provider to determine patient risk as a function of operator experience level.

14. CONCLUSIONS

The data presented in the this PMA characterize the safety and effectiveness of the SAPIEN Transcatheter Heart Valve when used to treat patients with severe aortic stenosis who have been determined by a cardiac surgeon to be at high risk (>15% risk of mortality) for open aortic valve

replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis. A number of analyses both pre-specified and *post hoc* have been presented to allow for a complete assessment of the totality of the data. The Panel will be asked to fully assess the significance of both the statistical and clinical results in order to render a recommendation for the benefit to risk profile of using the SAPIEN Transcatheter Heart Valve to treat these patients.

15. APPENDIX

The following table summarizes the data utilized in developing the Kaplan-Meier curves for the primary endpoint.

Table 30 - Summary Table for All-Cause Mortality at 24 Months (ITT Population)

				Cumulative number of			95% CI			95% CI	
Population	Treatment	Time (months)	No of patients at risk	Events	Censoring	Event rate (%)	Lower Limit	Upper Limit	Survival rate (%)	Lower Limit	Upper Limit
ITT	TAVR	0	348	0	0	0.00	0.00	0.00	100.00	100.00	100.00
		4	305	42	1	12.09	8.66	15.51	87.91	84.49	91.34
		8	281	64	3	18.45	14.37	22.54	81.55	77.46	85.63
		12	260	84	4	24.27	19.75	28.79	75.73	71.21	80.25
		16	243	94	11	27.23	22.53	31.93	72.77	68.07	77.47
		20	224	109	15	31.75	26.81	36.68	68.25	63.32	73.19
		24	172	116	60	33.92	28.89	38.95	66.08	61.05	71.11
	AVR	0	351	0	0	0.00	0.00	0.00	100.00	100.00	100.00
		4	266	63	22	18.79	14.61	22.98	81.21	77.02	85.39
		8	246	79	26	23.70	19.13	28.27	76.30	71.73	80.87
		12	236	89	26	26.80	22.03	31.58	73.20	68.42	77.97
		16	224	96	31	29.00	24.10	33.90	71.00	66.10	75.90
		20	210	106	35	32.20	27.14	37.26	67.80	62.74	72.86
		24	165	114	72	34.96	29.75	40.16	65.04	59.84	70.25

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